ASSESSMENT REPORT ON

TOLUENE

FOR DEVELOPING AMBIENT AIR QUALITY OBJECTIVES

Alberta
Environment

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TOLUENE

FOR DEVELOPING AN AMBIENT AIR QUALITY OBJECTIVES

Prepared by
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IN CONJUNCTION WITH
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for
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FOREWORD

Alberta Environment maintains Ambient Air Quality Objectives[1] to support air quality management in Alberta. Alberta Environment currently has ambient objectives for more than thirty substances and five related parameters. These objectives are periodically updated and new objectives are developed as required.

With the assistance of the Clean Air Strategic Alliance, a multi-stakeholder workshop was held in October 2000 to set Alberta's priorities for the next three years. Based on those recommendations and the internally identified priority items by Alberta Environment, a three-year work plan ending March 31, 2004 was developed to review four existing objectives, create three new objectives for three families of substances, and adopt six new objectives from other jurisdictions.

In order to develop a new three-year work plan, a multi-stakeholder workshop was held in October 2004. This study was commissioned in preparation for the workshop to provide background information on alternative, science based, and cost effective methods for setting priorities.

This document is one of a series of documents that presents the scientific assessment for these adopted substances.

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[1] **NOTE**: The *Environmental Protection and Enhancement Act*, Part 1, Section 14(1) refers to "ambient environmental quality objectives" and uses the term "guidelines" in Section 14(4) to refer to "procedures, practices and methods for monitoring, analysis and predictive assessment." For consistency with the *Act*, the historical term "ambient air quality guidelines" is being replaced by the term "ambient air quality objectives." This document was prepared as the change in usage was taking place. Consequently any occurrences of "air quality guideline" in an Alberta context should be read as "air quality objective."

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ACRONYMS, ABBREVIATIONS, AND DEFINITIONS

AAL	Allowable Ambient Level (Massachusetts) or Acceptable Ambient Level (North Carolina)
AAQC	Ambient Air Quality Criteria
AAS	Ambient Air Standard (Louisiana)
ACGIH	American Conference of Governmental Industrial Hygienists
AGC	Annual Guideline Concentration (New York State)
ANR	Vermont Agency of Natural Resources (Vermont)
ASIL	Acceptable Source Impact Level (Washington Department of Ecology)
ATC	Allowable Threshold Concentration – continuous exposure (daily lifetime) (Massachusetts DEP)
ATSDR	Agency for Toxic Substances and Disease Registry
bw	body weight
CalEPA	California Environmental Protection Agency
CAPCOA	California Air Pollution Control Officers Association
CAS	Chemical Abstracts Service
CCME	Canadian Council of Ministers of the Environment
CEIL	Ceiling Value
CEPA	Canadian Environmental Protection Act
DEC	Department of Environmental Conservation (*e.g.*, New York)
DENR	Department of Environment and Natural Resources (*e.g.*, North Carolina)
DEP	Department of Environmental Protection (*e.g.*, Massachusetts, New Jersey)
DES	Department of Environmental Services (*e.g.*, New Hampshire)
DEQ	Department of Environmental Quality (*e.g.*, Michigan, Louisiana, Oklahoma
DOE	Department of Environment or Department of Ecology (*e.g.*, Washington)
ENEV	Estimated No-Effects Value
EPA	Environmental Protection Agency (*e.g.*, Ohio)
ESL	Effects Screening Level
GLC	Ground Level Concentration
GV	Guideline Value
HAAS	Hazardous Ambient Air Standard
HEAST	Health Effects Assessment Summary Tables
HEC	Human Equivalent Concentration
HRV	Health Risk Value
IARC	International Agency for Research on Cancer
IHRV	Inhalation Risk Value
IRIS	Integrated Risk Information System
IRSL	Initial Risk Screening Level
ITSL	Interim Threshold Screening Level
LC50	Median Lethal Concentration
LD50	Median Lethal Dose
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEC	Lowest-Observed-Effect Concentration
LOEL	Lowest-Observed-Effect Level
MAAC	Maximum Acceptable Ambient Air Concentration

MAAQC	Maximum Annual Air Quality Criteria
MAC	Maximum Acceptable Concentration
MACT	Maximum Achievable Control Technology
MAGLC	Maximum Acceptable Ground-Level Concentration
MAQC	Maximum Air Quality Criteria
MDH	Minnesota Department of Health
MHRV	Multimedia Health Risk Value
MIC	Maximum Immission Concentration (Netherlands)
MPR	Maximum Permissible Risk Level
MRL	Minimal Risk Level
MTLC	Maximum Tolerable Level Concentration
NAAQO	National Ambient Air Quality Objective
NIEHS	National Institute of Environmental Health Sciences (USA)
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-Observed-Adverse-Effect Level
NOEC	No-Observed-Effect Concentration
NOEL	No-Observed-Effect Level
NPRI	National Pollutant Release Inventory
NRCC	Natural Resource Conservation Commission
NTP	National Toxicology Program (USA)
OEHHA	Office of Environmental Health Hazard Assessment (California EPA)
OEL	Occupational Exposure Limit
OMOE	Ontario Ministry of Environment
OSHA	Occupational Safety and Health Association
PEL	Permissible Exposure Limit
PM	Particulate Matter
POI	Point of Impingement
PSL	Priority Substance List
PSL1	First Priority Substances List (Canada)
PSL2	Second Priority Substances List (Canada)
RD50	Median Respiration Rate Decrease
REL	Either Reference Exposure Limit as used by the California EPA or Recommended Exposure Limit used by both NIOSH and ATSDR
RfC	Reference Concentration
RfD	Reference Dose
RIVM	Netherlands Research for Man and Environment
RM	Risk Management
RTECS	Registry of Toxic Effects of Chemical Substances
SGC	Short-term Guideline Concentration
SRSL	Secondary Risk Screening Level
STEL	Short-term Exposure Limit
TAPG	Toxic Air Pollutant Guideline
T-BACT	Best Available Control Technology for Toxics
TC	Tolerable Concentration
TCA	Tolerable Air Concentration

TC01	Tumorigenic Concentration - the concentration of a contaminant in air generally associated with a 1% increase in incidence or mortality due to tumours
TC05	Tumorigenic Concentration - the concentration of a contaminant in air generally associated with a 5% increase in incidence or mortality due to tumours
TD05	Tumorigenic Dose - the total intake of a contaminant generally associated with a 5% increase in incidence or mortality due to tumours
TEL	Threshold Effects Exposure Level
TLV	Threshold Limit Value
TNRCC	Texas Natural Resource Commission
TWA	Time-Weighted-Average
U.S. EPA	United States Environmental Protection Agency
WHO	World Health Organization

ppm	parts per million
ppb	parts per billion
mg	a milligram, one thousandth of a gram
µg	a microgram, one millionth of a gram
ng	a nanogram, one billionth of a gram

SUMMARY

Toluene is a clear, colourless, volatile and flammable liquid under standard conditions. It is a naturally occurring component of crude oil and petroleum. Toluene is also formed during the combustion of organic materials; thus forest, grass and other biomass fires will release toluene to the atmosphere. The manufacturing of toluene occurs primarily *via* isolation from petroleum mixtures by the distillation of reformed or pyrolyzed petroleum and coal-tar oil. The primary use of isolated toluene in Canada is in the production of benzene by hydrodealkylation. Toluene is widely used as a solvent in paints, varnishes, pesticide formulations, printing inks, dyes, adhesives, sealants, cleaning agents, nail polish, and for chemical extractions. Toluene also is used as a feedstock or starting material in the synthesis of various organic chemicals.

The largest source of toluene release to the environment is the production, transport, use and disposal of gasoline, and other industrial and consumer products that contain toluene. Roughly 99% of toluene released to the environment will occur in the atmosphere.

Toluene is expected to exist solely as a vapour in the ambient atmosphere. Vapour-phase toluene is rapidly degraded in the atmosphere *via* reaction with photochemically-produced hydroxyl radicals, nitrate radicals and ozone molecules, with the reaction with hydroxyl radicals being the most significant fate process. The half-lives for the reaction with hydroxyl radicals are estimated to range from 4.5 hours to 10 days.

The major sectors in Alberta that release toluene to air are the oil and gas sector (including oil sands operations, gas plants, and petroleum refineries) and cement manufacturing. For the majority of these facilities, fugitive emissions comprise the most significant portion of toluene emissions to air, although stack emissions, and releases during storage and handling can also contribute significantly to toluene air emissions, depending on the facility.

Toluene is rapidly absorbed from the lungs following inhalation exposure. Once absorbed, it is rapidly distributed to lipid-rich and highly vascular tissues such as the brain. Toluene is metabolized in humans and animals *via* an initial side-chain hydroxylation reaction (to form benzyl alcohol). Following this, benzyl alcohol is oxidized to benzoic acid, which is then conjugated with glycine to form hippuric acid. Hippuric acid is the primary end product of toluene metabolism in both humans and laboratory animals. The liver is thought to be the primary site of toluene metabolism. In both humans and laboratory animals, toluene absorbed *via* inhalation is rapidly excreted in the urine as hippuric acid. Roughly 75 to 80% of the inhaled toluene that is absorbed can be accounted for as hippuric acid in the urine. Much of the remaining portion is exhaled as the parent compound. The excretion of un-metabolized toluene in exhaled air can represent up to 20% of absorbed toluene. Less than 2% of inhaled toluene is excreted in the feces.

Adverse effects on the central nervous system are the critical effects of concern following acute human inhalation exposure to toluene. Symptoms of acute exposure progress from fatigue, headache, and decreased manual dexterity to narcosis as exposure increases. Depression, memory loss, impaired coordination and reaction time also occur with increasing exposure.

Respiratory tract irritation is also commonly reported in acute inhalation studies with both humans and experimental animals.

Performance deficits in neurobehavioural tests have been observed in studies with human volunteers acutely exposed to controlled toluene concentrations of >50 ppm (188 mg/m^3) and in laboratory animals repeatedly exposed to >500 ppm (1,875 mg/m^3) toluene. In the human volunteer studies, 50 ppm appears to be a threshold as acute exposure to toluene concentrations below 50 ppm results in few, if any, observable effects, but signs of neurological impairment have been observed with concentrations greater than 50 ppm. Inhalation of 100 to 200 ppm (375 to 750 mg/m^3) is associated with headaches and mild transient irritation of the upper respiratory tract; 400 ppm (1,500 mg/m^3) is associated with eye irritation, lacrimation and giddiness; 600 ppm (2,250 mg/m^3) with lethargy, giddiness and slight nausea; 800 ppm (3,000 mg/m^3) is associated with moderate to severe eye and upper respiratory tract irritation, drowsiness, nasal discharge, ataxia, dizziness and metallic taste in the mouth. The highest toluene air concentrations that can be tolerated for short durations (3.5 to 6 hours) without measurable neurobehavioural effects are 80 to 100 ppm (300 to 375 mg/m^3).

Current occupational exposure limits for toluene derived by ACGIH, NIOSH and OSHA are based on human studies where central nervous system toxicity and irritant effects were demonstrated at air concentrations above 40 ppm (150 mg/m^3).

It is well established that neurotoxicity and neurobehavioural deficits are the principal effects of long term inhalation exposure to toluene in both humans and experimental animals. Both the human and animal subchronic and chronic inhalation data generally indicate that no adverse neurological or neurobehavioural effects are likely to occur at toluene air concentrations lower than 50 ppm (188 mg/m^3). The major symptoms following subchronic or chronic inhalation exposure to toluene in humans include subtle changes in neurological functions including cognitive and neuromuscular performance, hearing and colour discrimination in chronically exposed workers. Subchronic or chronic studies with experimental animals also indicate that major symptoms of toluene exposure include behavioural changes, hearing loss and subtle changes in brain structure, brain electrophysiology and brain chemistry. Studies of occupationally exposed workers also indicate that chronic exposure to toluene concentrations ranging from 30 to 130 ppm (113 to 488 mg/m^3) can lead to deficits in hearing and colour vision. Hearing loss also has been reported in experimental animals exposed to 700 to 1,500 ppm (2,625 to 5,625 mg/m^3) toluene.

There are few human studies available that investigated the reproductive or developmental effects of toluene following inhalation exposure. Overall, the human data that exists do not provide convincing evidence that toluene causes reproductive effects in humans. A number of developmental toxicity studies with rats, mice and rabbits exposed *via* inhalation to toluene indicate that toluene is not a potent teratogen at exposure levels below those that induce maternal toxicity, but it can retard fetal growth and skeletal development and cause behavioural alterations in offspring.

The results of *in vivo* studies of exposed humans and *in vitro* assays with bacteria and various other test systems generally indicate that toluene is probably not mutagenic or genotoxic. There is no convincing evidence that toluene has carcinogenic activity in either humans or experimental animals.

For agencies with existing ambient air quality guidelines for toluene, the guidelines, for the most part, are based on the U.S. EPA RfC of 0.4 mg/m^3, the ACGIH TLV-TWA values of 50 ppm (188 mg/m^3) or the NIOSH REL-TWA value of 100 ppm (375 mg/m^3) (adjusted with various modifying and uncertainty factors). Ontario, Quebec and the World Health Organization have developed ambient air guidelines that are based on odour effects of toluene, rather than health effects data. Odour thresholds for toluene are highly variable and have been reported to range from as low as 0.016 ppm to 69.2 ppm (0.06 to 260 mg/m^3). All existing air quality guideline values appear to be adequately protective of human health over their respective averaging periods. In addition, given the available data on the environmental fate, transport and effects of toluene, this compound is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone or alter precipitation patterns. No specific information on the photochemical smog formation potential of toluene was identified; however, it would be expected to have a similarly low to moderate smog formation potential as ethylbenzene and xylenes.

1.0 INTRODUCTION

Alberta Environment (AENV) establishes Ambient Air Quality Objectives under Section 14 of the Environmental Protection and Enhancement Act (EPEA). These guidelines are part of the Alberta Air Quality Management System (AENV, 2000a).

Ambient Air Quality Objectives (AAQO) provide the basis for determining whether or not ambient air quality is acceptable from a health perspective. For substances lacking Alberta objectives, the development of acceptable ambient air concentrations typically considers a number of factors, including physical-chemical properties, sources, effects on human and environmental health, air monitoring techniques and ambient air guidelines derived by other jurisdictions within Canada, the United States, various other countries and multi-country organizations such as the World Health Organization.

The main objective of this assessment report is to provide a review of scientific and technical information to assist in evaluating the basis and background for an Ambient Air Quality Objective for toluene. The following aspects were examined as part of this review:

- Physical and chemical properties
- Existing and potential natural and anthropogenic emissions sources in Alberta
- Effects on humans, animals and vegetation
- Monitoring techniques
- Ambient air guidelines in other Canadian jurisdictions, United States, European Union and Australia and the basis for their development and use

Key physical and chemical properties that govern the fate and behaviour of toluene in the environment are reviewed and presented in this assessment report. Existing and potential natural and anthropogenic sources of toluene air emissions in Alberta are presented in this report. This included information obtained from Environment Canada's National Pollutant Release Inventory (NPRI) and the National Air Pollution Surveillance (NAPS) Network.

Scientific information regarding the toxic effects of toluene on humans and animals is reported in a number of sources, including toxicological and epidemiological studies published in peer-reviewed journals and detailed regulatory agency reviews such as those published by the International Agency for Research on Cancer (IARC), World Health Organization (WHO), U.S. Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Environmental Protection Agency's (U.S. EPA) Integrated Risk Information System (IRIS) and Toxicological Profiles and Canadian Priority Substance List Reports under CEPA (1999). There is also a recent air quality guideline scientific support document for toluene from the Ontario Ministry of the Environment (OMOE, 2001). These sources provide valuable information for understanding the potential human and environmental health effects of toluene. Key information from these sources regarding the effects of airborne concentrations of toluene on humans, animals, plants and the environment is summarized in this report.

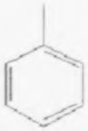
Air monitoring and measuring techniques for toluene in air are well documented in the peer-reviewed scientific and regulatory agency literature. Several widely used and accepted air monitoring reference methods exist for toluene that have been developed, tested and reported by such agencies as U.S. EPA, U.S. National Institute of Occupational Safety and Health (NIOSH) and U.S. Occupational Safety and Health Administration (OSHA). These methods and techniques are summarized in this report.

2.0 GENERAL SUBSTANCE INFORMATION

Toluene is a clear, colourless, volatile liquid under standard conditions (ATSDR, 2000; CEPA, 1992; HSDB, 2003; WHO, 1986). Its odour has been most commonly described as sour or burnt (AIHA, 1989; Verschueren, 1983), or sweet and pungent (ATSDR, 2000; CEPA, 1992). Toluene is moderately soluble in water and is miscible with most organic solvents (Budavari *et al.*, 1989; CEPA, 1992; ATSDR, 2000). This substance is not corrosive and does not react with dilute acids or bases, but it will react violently with nitric and sulphuric acids (DHSS, 1998; WHO, 1986). Toluene is not compatible with strong oxidisers such as chlorine, bromine and fluorine (DHSS, 1998). Toluene is a highly flammable liquid and is explosive at room temperature and standard atmospheric pressure (CEPA, 1992; WHO, 1986).

Table 1 provides a list of common synonyms, trade names and identification numbers for toluene.

Table 1 Identification of Toluene

Property	Value
Formula	C_7H_8
Structure	
CAS Registry Number	108-88-3
RTECS Number	XS5250000
UN Number	UN1294
Common Synonyms	antisal 1a methyl-benzene methylbenzol monomethyl benzene phenyl methane tol toluol tolu-sol
Tradenames	Methacide EPA hazardous waste U220 OHM/TADS 7216928 IMCO 3.2 NCI CO7272

Toluene is a naturally occurring component of crude oil and petroleum (CEPA, 1992). It is isolated from petroleum mixtures by the distillation of reformed or pyrolyzed petroleum and coal-tar oil (ATSDR, 2000). Depending on the grade and purity of toluene, a number of other chemicals can be present in commercial toluene formulations, including benzene, xylenes and PAHs (ACGIH, 1992). In Canada, toluene is not added intentionally to gasoline during blending; rather, it is present in gasoline as the result of normal petroleum refining processes (CEPA, 1992). The average toluene content of gasoline is 8.3% by weight (CEPA, 1992).

The primary use of isolated toluene in Canada is in the production of benzene by hydrodealkylation (CEPA, 1992). Toluene is widely used as a solvent in paints, varnishes, pesticide formulations, printing inks, adhesives, sealants, cleaning agents and for chemical extractions (ATSDR, 2000; CEPA, 1992). Toluene is used also as a feedstock or starting material in the synthesis of trinitrotoluene (TNT) and a number of other organic chemicals, such as nylon and polyurethanes (ATSDR, 2000). Toluene is used in the manufacturing of pharmaceuticals, dyes, nail polish and a number of other consumer products (ATSDR, 2000). Its presence in various consumer products can result in indoor air concentrations of toluene being much higher than ambient outdoor air concentrations. Cigarette smoke also is a major source of toluene; up to 60 µg toluene/kg body weight/day can come from cigarette smoking (CCME, 2003).

2.1 Physical, Chemical and Biological Properties

The physical and chemical properties of toluene are summarized in Table 2.

Table 2 Physical and Chemical Properties of Toluene

Property	Value	Reference
Molecular Weight	92.13	Mackay *et al.*, 1992; WHO, 1986
Physical State	Liquid	ATSDR, 2000; CEPA, 1992; Verschueren, 1983; WHO, 1986;
Melting Point	-94.9°C	HSDB, 2003; RAIS, 2003
	-95°C	ATSDR, 2000; Mackay *et al.*, 1992; WHO, 1986
	-95.1°C	Verschueren, 1983
Boiling Point	110.6°C	ATSDR, 2000; HSDB, 2003; Mackay *et al.*, 1992; RAIS, 2003; WHO, 1986
	110.8°C	Verschueren, 1983
Specific Gravity (liquid)	0.8623 at 20°C	WHO, 1986
	0.8636 at 20°C	HSDB, 2003
	0.867 at 20°C	Verschueren, 1983
Specific Gravity (gas; air=1)	3.10	Clayton and Clayton, 1994
	3.14	Verschueren, 1983
	3.20	WHO, 1986
Vapour Pressure	3.7 kPa at 25°C	CEPA, 1992
	3.79 kPa at 25°C	HSDB, 2003; RAIS, 2003
	3.83 kPa at 25°C	WHO, 1986
Solubility in Water	515 mg/L at 20°C	Verschueren, 1983
	526 mg/L at 25°C	HSDB, 2003; RAIS, 2003
	534.8 mg/L at 25°C	Howard, 1990
	535 mg/L at 25°C	WHO, 1986; CEPA, 1992
Solubility	Miscible with other organic solvents	Budavari *et al.*, 1989; CEPA, 1992

Property	Value	Reference
Henry's Law Constant	0.00664 atm.m^3/mole at 25°C	HSDB, 2003
	0.00594 atm.m^3/mole at 25°C	Howard, 1990
Octanol Water Partitioning Coefficient (log K_{ow})	2.69	CEPA, 1992; Verschueren, 1983; WHO, 1986
	2.72	Howard, 1990
	2.73	HSDB, 2003
Octanol Carbon Partitioning Coefficient (log K_{oc})	1.57 to 2.25	Howard, 1990
	2.22	HSDB, 2003
Flash Point (closed cup)	4°C	ATSDR, 2000
	4.4°C	WHO, 1986
Explosive Limits	1.3% (lower)	ATSDR, 2000
Autoignition Temperature	480°C	ATSDR, 2000
	552°C	WHO, 1986
Odour Threshold	0.016 to 37.2 ppm (detection)	van Gemert, 1999
	0.93 to 69.2 ppm (recognition)	van Gemert, 1999
	1.6 ppm (geometric mean)	AIHA, 1989
	2.5 ppm	WHO, 1986
	2.9 ppm	Amoore and Hautala, 1983
Bioconcentration Factor in Fish	13 to 90	HSDB, 2003
Conversion Factors for Vapour (at 25°C and 101.3 kPa)	1 ppm = 3.75 mg/m^3 1 mg/m^3 = 0.266 ppm	WHO, 1986

2.2 Environmental Fate

The environmental fate of toluene is summarized in Table 3. Large amounts of toluene enter the environment each year, primarily as direct releases to the atmosphere. The largest source of toluene release is the production, transport and use of gasoline although significant quantities are released from the production, use and disposal of industrial and consumer products that contain toluene (ATSDR, 2000). Fugacity modelling indicates that roughly 99% of toluene released to the environment will occur in the atmosphere (Mackay *et al.*, 1992).

Due to its high vapour pressure, toluene is expected to exist solely as a vapour in the ambient atmosphere (HSDB, 2003; ATSDR, 2000). As it is moderately soluble in water, some toluene may be removed from the atmosphere by wet deposition; however, no quantitative estimates for this fate process appear to be available (ATSDR, 2000). Vapour-phase toluene is rapidly degraded in the atmosphere *via* reaction with photochemically-produced hydroxyl radicals, nitrate radicals and ozone molecules (HSDB, 2003). The reaction with hydroxyl radicals is the most significant fate process for toluene and yields cresol and benzaldehyde, which in turn undergo ring cleavage to yield a variety of carbonyl compounds and simple hydrocarbons (Davis *et al.*, 1979; Hoshino *et al.*, 1978; Kenley *et al.*, 1973). The half-lives for the reaction with hydroxyl radicals, the night time reaction with nitrate radicals and for the reaction with ozone are estimated to be 4.5 hours to 10 days (Howard *et al.*, 1991; Finlayson-Pitts and Pitts, 1986), 491 days and 27,950 days, respectively (HSDB, 2003). The night time reaction with nitrate radicals yields benzyl nitrate and nitrotoluene (Atkinson 1990). Photolysis is not considered to be an environmentally significant fate process for toluene (Mackay *et al.*, 1992).

Table 3 Environmental Fate of Toluene (based on Mackay *et al.*, 1992; HSDB, 2003; Howard, 1990)

System	Fate	Half-life
Water	Loss by volatilization and aerobic biodegradation; moderate adsorption to sediment or suspended particulate matter; potential bioconcentration in aquatic organisms; hydrolysis is negligible	*Volatilization*: one hour (model river) and 4 days (model lake) *Aqueous aerobic biodegradation*: 96 hours to 22 days
Soil	Loss *via* volatilization from dry and moist soil and aerobic biodegradation; moderate adsorption; moderate to high mobility; potential for leaching	*Aqueous aerobic biodegradation*: 96 hours to 22 days
Air	Exists solely as a vapour; degradation *via* reaction with hydroxyl radicals, nitrate radicals and ozone molecules; photolysis is negligible	*Photochemical reactions with hydroxyl radicals*: 3 days *Photochemical reactions with nitrate radicals*: 491 days *Photochemical reactions with ozone molecules*: 27,950 days

Due to its short atmospheric residence time and inability to absorb ultraviolet radiation, toluene is not associated with stratospheric ozone depletion or global warming (NRC, 1980).

Volatilization is the most important fate process for toluene from both dry and wet soil surfaces. Although the rate of volatilization from soils depends on temperature, humidity and soil type, typically greater than 90% of the toluene in the upper soil layer volatilizes to air within 24 hours (Balfour *et al.*, 1984; Thibodeaux and Hwang, 1982). Toluene present in deeper soil layers is much less likely to volatilize. Volatilization half lives for toluene in soil range from nine seconds (at soil surface) to <1 month for wet soil at depths of 10 cm (CEPA, 1992). Volatilization occurs most rapidly in dry surficial soils; wet soils retain toluene for longer durations due to its moderate water solubility. Toluene is considered to have a high to moderate mobility in soil (HSDB, 2003). Its Log K_{OC} value indicates that toluene mobility will be moderately retarded by adsorption to soils rich in organic matter, but toluene will readily leach to groundwater in soils that are low in organic carbon content (Wilson *et al.*, 1981). After volatilization, biodegradation is the next most important fate process for toluene in soil, particularly for toluene present in subsurface soil. Biodegradation half-lives for toluene in soil are estimated to range from as short as one hour, to as long as 22 days depending on soil conditions (Mackay *et al.*, 1992; Howard *et al.*, 1991; ATSDR, 2000).

Volatilization is the most significant fate process for toluene in surface waters. The rate of toluene volatilization from surface waters depends greatly on whether the water is static (half-life ranging from one to 16 days) or turbulent (half-life ranging from five to six hours) (Mackay and Leinonen, 1975; Wakeham *et al.*, 1983). Other reported half-lives for volatilization from water range from as low as 36 minutes in fast flowing water to as high as 47 days in stagnant water (Howard, 1990; U.S. EPA, 1987). In water, any toluene that does not volatilize is expected to adsorb to suspended solids and sediments (ATSDR, 2000). Hydrolysis is not expected to be a significant fate process (Mackay *et al.*, 1992). Toluene may be oxidized in water by reactions similar to those that occur in air, although the rates of these reactions in water are very slow, relative to other fate processes such as volatilization and biodegradation (*i.e.*, 13 to 54 days estimated based on aqueous reaction of benzene with hydroxyl radicals in water; Howard *et al.*, 1991). The aqueous aerobic biodegradation half-life of toluene in water is estimated to range from 96 hours to 528 hours (Mackay *et al.*, 1992). Biodegradation in surface waters is dependent on a multitude of factors such as temperature, oxygen levels, nutrients, pH, duration of microbial acclimation, *etc.* (ATSDR, 2000).

Toluene is expected to have a low tendency to bioconcentrate in aquatic organisms (Franke *et al.*, 1994). Reported aquatic organism BCFs range from 1 to 380 (CEPA, 1992). The amount of toluene that accumulates in aquatic species also depends on the degree to which the species metabolize toluene. All non-plant aquatic and terrestrial organisms are capable of at least limited toluene metabolism. This metabolism limits the ability of toluene to bioaccumulate to high concentrations and to biomagnify in aquatic and terrestrial food webs.

3.0 EMISSION SOURCES AND INVENTORIES

3.1 Natural Sources

Toluene is a naturally occurring component of crude oil and petroleum (CEPA, 1992). Toluene is formed during the combustion of organic materials; thus forest, grass and other biomass fires will release toluene to the atmosphere.

3.2 Anthropogenic Sources and Alberta Emissions Inventory

3.2.1 Industrial

Production processes, as well as industrial, commercial and domestic sources and uses of toluene were described in Section 2.0.

A total of 97 industrial facilities in Alberta reported on-site releases of toluene to the 2001 National Pollutant Release Inventory (NPRI) database. Of the total reported environmental releases of toluene, the majority is released into the atmosphere, although some facilities in Alberta also release toluene to land. For example, the Petro-Canada Refinery in Edmonton reported 13.92 tonnes released to land of the total 19.60 tonnes released to the environment (5.67 tonnes were released to air) (NPRI, 2001).

Table 4 provides a summary of on-site releases for the top 10 facilities in Alberta that released toluene to air for the 2001 reporting year. Table 5 provides details on the air emissions for these facilities. The major sectors in Alberta that release toluene to air are the oil and gas sector (including oil sands operations, gas plants and petroleum refineries) and cement manufacturing. For the majority of these facilities, fugitive emissions comprise the most significant portion of toluene emissions to air, although stack emissions and releases during storage and handling can also contribute significantly to toluene air emissions, depending on the facility (See Table 5). For some facilities (*e.g.*, Lafarge Canada Inc. and a number of gas plants), stack emissions of toluene are either the sole or primary point of release to the atmosphere.

Table 4 Total On-site Releases (tonnes/year) of Toluene in Alberta (Ten Largest Contributors) According to NPRI, 2001

NPRI ID	Facility Name	Location	Total Releases (tonnes/year) Air	Land	Water	Total
2274	Syncrude Canada Ltd. - Mildred Lake Plant Site	Fort McMurray	210.29	0	0	210.29
2230	Suncor Energy Inc. - Suncor Energy Inc. Oil Sands	Fort McMurray	114.66	0.02	0	114.68
5291	Lafarge Canada Inc - Exshaw Plant	Exshaw	23.80	0	0	23.80
2960	Shell Canada Products - Shell Scotford Refinery	Fort Saskatchewan	22.07	5.64	0	27.71
4152	BP Canada Energy Company - West Pembina Gas Plant	Drayton Valley	12.53	0	0	12.53
3707	Imperial Oil - Strathcona Refinery	Edmonton	10.44	2.69	0	13.13
0432	Devon Canada Corporation - Wapiti Gas Plant	Grande Prairie	9.93	11.47	0	21.40
3937	ExxonMobil Canada Ltd. - Carson Creek Cycling Plant	Whitecourt	9.54	0.76	0	10.30
1881	Parkland Refining Ltd. - Bowden Refinery	Bowden	7.71	0.02	0	7.73
4566	Pengrowth - Judy Creek Production Complex	Swan Hills	7.17	0.02	0	7.19

Table 5 Air Emissions of Toluene (tonnes/year) for Ten Largest Contributors in Alberta According to NPRI, 2001

NPRI ID	Facility Name	Location	Air Emissions (tonnes/year)					
			Stack/ Point	Storage/ Handling	Fugitive	Spills	Other	Total
2274	Syncrude Canada Ltd. - Mildred Lake Plant Site	Fort McMurray	3.04	12.88	194.37	0	0	210.29
2230	Suncor Energy Inc. - Suncor Energy Inc. Oil Sands	Fort McMurray	3.80	1.50	109.36	0	0	114.66
5291	Lafarge Canada Inc - Exshaw Plant	Exshaw	23.80	0	0	0	0	23.80
2960	Shell Canada Products - Shell Scotford Refinery	Fort Saskatchewan	0	1.39	20.68	0	0	22.07
4152	BP Canada Energy Company - West Pembina Gas Plant	Drayton Valley	12.53	0	0	0	0	12.53
3707	Imperial Oil - Strathcona Refinery	Edmonton	0.88	4.08	5.45	0	0.03	10.44
0432	Devon Canada Corporation - Wapiti Gas Plant	Grande Prairie	9.27	0.03	0.63	0	0	9.93
3937	ExxonMobil Canada Ltd. - Carson Creek Cycling Plant	Whitecourt	9.26	0	0.28	0	0	9.54
1881	Parkland Refining Ltd. - Bowden Refinery	Bowden	0	2.93	4.65	0.13	0	7.71
4566	Pengrowth - Judy Creek Production Complex	Swan Hills	6.81	0.22	0.14	0	0	7.17

3.3 Alberta Ambient Air Concentrations

Limited data on ambient air concentrations of toluene in Alberta are available from National Air Pollutant Surveillance (NAPS) Network sites. Toluene air data for 2001 are available for three monitoring locations in the most recent annual summary of NAPS data (NAPS, 2002): 17 Street and 105 Avenue (Edmonton); 10255 104 Street (Edmonton); and 611 Fourth Street S.W. (Calgary). At the 17 Street and 105 Avenue (Edmonton) location, toluene air concentrations ranged from 0.6 to 9.5 $\mu g/m^3$ (annual mean = 3.3 $\mu g/m^3$). At the 10255 104 Street (Edmonton) location, toluene air concentrations ranged from 1.3 to 25.1 $\mu g/m^3$ (annual mean = 4.5 $\mu g/m^3$). At the 611 Fourth Street S.W. (Calgary) location, concentrations ranged from 1.0 to 15.6 $\mu g/m^3$ (annual mean = 4.0 $\mu g/m^3$).

Alberta Environment has conducted a number of air quality monitoring surveys over the past several years in various regions of Alberta. Some of these surveys have reported ambient air concentrations of toluene. For example, a survey conducted from October 2000 to June 2001 in the Whitemud Drive area of Edmonton reported that one-hour average ambient air concentrations of toluene ranged from <2 to 22 $\mu g/m^3$ (AENV, 2002a). A volatile organic compound (VOC) survey in the Fort Saskatchewan/Redwater area (AENV, 2003) conducted from May 2001 to February 2002 reported one-hour average toluene air concentrations ranging from 0.24 to 3.83 $\mu g/m^3$ (average = 1.74 $\mu g/m^3$). A survey conducted in the Town of Banff in November, 2002 reported one-hour average toluene concentrations on two sampling days of 2.79 and 5.01 $\mu g/m^3$ (AENV, 2002b). Toluene one-hour average concentrations ranged from non-detectable to 2 $\mu g/m^3$ in an air monitoring survey conducted in the Carstairs/Crossfield Area between December 1999 and March 2000 (AENV, 2000b). A study of VOC air concentrations was conducted in the County of Grande Prairie between 1998 and 2000 (AENV, 2001). At a regional background location (Beaverlodge Agriculture Research Farm), 24-hour average toluene air concentrations ranged from <0.07 to 1.5 $\mu g/m^3$. Toluene air concentrations also were measured at stations near a number of gas plants, batteries and well sites. One-hour average toluene concentrations were reported to range from <1.4 to 198.6 $\mu g/m^3$. Twenty-four hour average toluene air concentrations were reported to range from 0.1 to 13.0 $\mu g/m^3$.

4.0 EFFECTS ON HUMANS AND ECOLOGICAL RECEPTORS

4.1 Humans and Experimental Animals

The following toxicological review of toluene is focussed primarily on the inhalation route of exposure, as this is the predominant route of human exposure to toluene in air. Data on other exposure routes are included in this review only where considered relevant or where inhalation exposure data are lacking. Where sufficient data are available, human studies are emphasized in this section. However, relevant experimental animal studies are included where human data is either lacking or inadequate.

4.1.1 Overview of Toxicokinetics of Toluene

Absorption

Toluene is rapidly absorbed from the lungs following inhalation exposure. Low *et al.* (1988) reported an absorption efficiency range of 50 to 80% in both animals and humans. Lof *et al.* (1993) reported that approximately 50% of radiolabelled toluene was absorbed from the lungs in volunteers exposed to 53 ppm (199 mg/m^3) for two hours during a period of light exercise. Seven human volunteers exposed to 50 ppm toluene in a closed chamber retained 83% of the inspired concentration on average (Benoit *et al.*, 1985).

Distribution

Once absorbed, toluene is transported throughout the body by red blood cells and appears to be associated with the hemoglobin rather than the cell membrane. It is hypothesized that toluene interacts with the hydrophobic core of the heme protein (ATSDR, 2000).

Absorbed toluene is rapidly distributed to lipid-rich and highly vascular tissues such as the brain (Sato and Nakajima, 1978; ATSDR, 2000). Due to its lipophilicity, toluene tends to accumulate in those areas of the brain that contain lipid-rich white matter (such as the brain stem) (Ameno *et al.*, 1992).

Toluene's affinity for lipid-rich tissue is supported by animal autoradiography studies. High levels of ^{14}C-labelled toluene were identified in the body fat, bone marrow, spinal nerves, spinal cord and white brain matter of exposed mice (Bergman, 1979). Similar studies in pregnant mice identified the preferential uptake of toluene into maternal brain and fat tissue. Distribution to the developing fetus appears to be limited, despite the relatively low molecular weight and lipophilic nature of toluene, which would otherwise suggest that the chemical might readily travel across the placental barrier. The preferential distribution to maternal adipose tissue is believed to be due to the lower lipid content in fetal tissues, relative to maternal tissues (Ghantous and Danielsson, 1986).

No studies were identified that examined *in vivo* distribution of toluene into breast milk of either humans or laboratory animals. However, the physical chemical properties of toluene suggest that partitioning into breast milk might occur.

Metabolism

Toluene is metabolized in humans and animals as follows. There is an initial side-chain hydroxylation of toluene (to form benzyl alcohol) that is catalyzed by the cytochrome P450 isozyme, CYP2E1. Following this, benzyl alcohol is oxidized to benzoic acid (ATSDR, 2000). Most of the benzoic acid is then conjugated with glycine to form hippuric acid (*i.e.*, the glycine conjugate of benzoic acid). Hippuric acid is the primary end product of toluene metabolism in both humans and laboratory animals (ATSDR, 2000). However, a small portion of the benzoic acid can be conjugated with UDP-glucuronate to form the acyl-glucuronide (ATSDR, 2000).

In humans and in rats, roughly 75 to 80% of the inhaled toluene that is absorbed can be accounted for as hippuric acid in the urine (Lof *et al.*, 1993; Wang and Nakajima, 1992). Much of the remaining portion is exhaled as the parent compound. A very small portion (<1 to 5%) can be converted by CYP1A2, CYP2B2 or CYP2E1 enzymes to *ortho-* or *para*-cresol, which are excreted in the urine as either sulphate or glucuronate conjugates (Baelum *et al.*, 1993, Nakajima *et al.*, 1997; Tassaneeyakul *et al.*, 1996).

After hippuric acid, the remaining urinary metabolites (in order of decreasing abundance) are: the glucuronyl conjugate of benzoic acid; sulphate and glucuronide conjugates of *ortho-* and *para*-cresol; S-benzylmercapturic acid; and S-*p*-toluylmercapturic acid (ATSDR, 2000).

Due to its high concentration of CYP isozymes relative to other tissues, the liver is thought to be the primary site of toluene metabolism (ATSDR, 2000).

As toluene is metabolized by relatively non-specific enzymes, it is not surprising that co-exposure to other organic solvents can alter the metabolism and subsequent toxicity of toluene. Hypothetically, compounds that stimulate or inhibit the metabolism of toluene may respectively decrease or increase toluene toxicity. Several metabolic interactions between toluene and other chemicals have been studied, with results indicating that alteration of toluene metabolism may influence toluene toxicity and that toluene also can influence the toxicity of a number of other chemicals. Various interactions have been studied with varying outcomes on toluene toxicity or the toxicity of other chemicals. These interactions are described in greater detail in ATSDR (2000).

Elimination and Excretion

The excretion of toluene and its metabolites occurs rapidly. Analyses of kinetic data for toluene concentrations in blood, exhaled air, or adipose tissue following inhalation exposure of humans and rats indicate that most absorbed toluene is rapidly eliminated from the body and that a smaller portion, which partitions to adipose tissue, is more slowly eliminated (ATSDR, 2000). In mice, toluene is quickly eliminated from alveolar air with a half-life of 2.6 hours while elimination from both blood and brain occurs even faster, with a biologic half-life of one hour. The half-life for toluene elimination from human adipose tissue is 0.5 to 2.7 days after inhaling 70 ppm (263 mg/m^3) for two hours (ACGIH, 1992).

In both humans and laboratory animals, toluene absorbed *via* inhalation is predominantly excreted in the urine as hippuric acid. Urinary excretion of *ortho*-cresol is about 1,000-fold lower than the excretion rate for hippuric acid (Baelum *et al.*, 1993).

As mentioned, roughly 75 to 80% of the inhaled toluene that is absorbed can be accounted for as hippuric acid in the urine (Lof *et al.*, 1993; Wang and Nakajima, 1992). Much of the remaining portion is exhaled as the parent compound. The excretion of un-metabolized toluene in exhaled air can represent up to 20% of absorbed toluene (Carlsson, 1982; Leung and Paustenbach, 1988; Lof *et al.*, 1993). Less than 2% of inhaled toluene is excreted in the feces (ACGIH, 1992). Under conditions in which the main pathway of toluene metabolism is inhibited by co-exposure to other organic substances, such as ethanol, exhalation of un-metabolized toluene can become the principal route of excretion (Baelum *et al.*, 1993).

Physiologically-Based Pharmacokinetic (PBPK) Models

A number of PBPK models are available that describe the kinetics of toluene after inhalation exposure. Two PBPK models have been developed for humans (*i.e.*, Fisher *et al.*, 1997; Pierce *et al.*, 1996; 1997) and three for rats (DeJongh and Blaauboer, 1996; 1997; Tardif *et al.*, 1993; van Asperen *et al.*, 2003). The majority of these models built upon the standard four-compartment PBPK model that was developed for styrene by Ramsey and Andersen (1984). The model by Pierce *et al.* (1996) accounts for such subject specific parameters as age, height, weight, alveolar ventilation rate, adipose tissue fraction and blood/air partition coefficients.

Fisher *et al.* (1997) developed another human PBPK model for volatile organic compounds that considers exposure to infants through lactation. It should be noted that no *in vivo* pharmacokinetic data are available and the resultant equations are based entirely on modelling. This model estimated that an infant would ingest 0.46 mg toluene/day *via* breast milk if the mother were occupationally exposed to 50 ppm (188 mg/m^3) of toluene (*i.e.*, the ACGIH threshold limit value – time weighted average) throughout a workday. This predicted daily intake for infants is less than the U.S. EPA Health Advisory of 2.0 mg/day that is based on a 10 kg child chronically drinking 1 L/day of toluene-contaminated water.

Dejongh *et al.* (1998) used their rat PBPK model for toluene and similar models for 14 other VOCs to demonstrate that the acute lethality of VOCs, including toluene, is directly related to the extent of their distribution into the brain.

Further information on these PBPK models can be found in the original papers and in the ATSDR (2000) report on toluene.

Mechanism of Toxic Action

In general, the mechanisms of action of toluene toxicity are not well understood, and for many effects, it is unclear whether toluene itself or its metabolites are responsible.

The mechanism for toluene's acute neurological effects on the central nervous system (CNS) is generally thought to involve reversible interactions between toluene (the parent compound) and lipids or proteins of cell membranes within CNS tissues (Franks and Lieb, 1985; 1987). On a molecular scale, it is postulated that toluene may intercalate into the lipid and protein matrix of cell membranes (ATSDR, 2000).

There is a hypothesis that chronic exposure to high concentrations of toluene brings about structural changes in the brain that are related to lipid compositional changes (ATSDR, 2000).

The mechanism of action underlying mild symptoms of neurological impairment are not well understood. One hypothesis postulates that repeated interaction of toluene with membrane proteins and/or phospholipids in brain cells can change activities of enzymes involved in the synthesis and/or degradation of neurotransmitters, and that altered levels of these neurotransmitters at particular sites in the brain may be responsible for the subtle neurological effects (ATSDR, 2000). Another hypothesis suggests that repeated exposure to toluene may cause neurological effects by changing the binding of certain neurotransmitters to cell membrane receptors (ATSDR, 2000).

Recent mechanistic studies have found that prenatal toluene exposure induces persistent oxidative changes and increases cell membrane fluidity in rat synaptosomes (Edelfors *et al.*, 2002) and that toluene can inhibit signal transduction at human acetylcholine receptors (Tsuga *et al.*, 2002).

Biomarkers

The American Conference of Governmental Industrial Hygienists (ACGIH, 2004) recommends using a combination of three biological exposure indices (*i.e.*, biomarkers) to assess exposure of workers to toluene in the workplace: *ortho*-cresol and hippuric acid levels in urine at the end of a workshift, and toluene levels in blood immediately prior to the last shift of a work week. Angerer *et al.* (1998) proposed that S-*p*-toluylmercapturic acid levels in urine may also be useful as a biological indicator of toluene exposure.

It should be recognized that a number of studies caution that there are substantial individual differences in the amount of these excreted metabolites, and that monitoring of urinary metabolites can only serve as a qualitative indication of exposure to toluene (Andersen *et al.*, 1983; Baelum *et al.*, 1987; Hasegawa *et al.*, 1983; Kawai *et al.*, 1996; Nise, 1992).

The most accurate and sensitive biomarker of toluene exposure is the presence of toluene itself in serum or blood (Kawai *et al.*, 1992a), but measurements of toluene or its metabolites in urine are often preferred due to the less invasive nature of urine sampling. Although measurement of urinary excretion of toluene metabolites is a less invasive method than blood sampling, the presence of these metabolites in the urine is not necessarily proof of toluene exposure since they also are products of normal endogenous metabolism (Baelum, 1990; Hjelm *et al.*, 1988; Lof *et al.*, 1993; Maestri *et al.*, 1997). In addition, background levels of these metabolites are also influenced by individual variability (Lof *et al.*, 1993), ethnic differences (Inoue *et al.*, 1986), alcohol consumption and smoking (Kawamoto *et al.*, 1996; Maestri *et al.*, 1997). Kawai *et al.* (1996) suggested that the presence of un-metabolized toluene in urine is a more sensitive biomarker for toluene exposure than the presence of hippuric acid or ortho-cresol.

Measurements of toluene in serum, blood and urine taken at the end of a shift all significantly correlate with measurements of toluene air concentrations from personal air monitors (Kawai *et al.*, 1992a; 1992b; 1996; Angerer and Kramer, 1997; Angerer *et al.*, 1998; Nise, 1992; Truchon *et al.*, 1996) and all have been commonly used as biomarkers of toluene exposure.

There are no reliable biomarkers for toluene exposure that persist in the body for an extended period of time after exposure has ceased (ATSDR, 2000). Nor are there any specific biomarkers of effect for toluene as a number of other organic solvents and other chemicals can cause similar neurological effects.

4.1.2 Acute Toxicity

Adverse effects on the CNS are the critical effects of concern following acute human inhalation exposure to toluene (ATSDR, 2000). Symptoms of acute exposure progress from fatigue, headache and decreased manual dexterity to narcosis with increasing exposure levels. Depression, memory loss, impaired coordination and reaction time also occur as exposure levels increase (ACGIH, 1992). Respiratory tract irritation is also commonly reported in acute inhalation studies with both humans and experimental animals. Degeneration of the nasal epithelium has been observed in animal studies.

Performance deficits in neurobehavioural tests have been observed in studies with human volunteers acutely exposed to controlled toluene concentrations of >50 ppm (188 mg/m^3) and in laboratory animals repeatedly exposed to >500 ppm (1,875 mg/m^3) toluene (ATSDR, 2000). In the human volunteer studies, 50 ppm appears to be a threshold as acute exposure to toluene concentrations below 50 ppm results in few, if any, observable effects, but signs of neurological impairment have been observed with concentrations greater than 50 ppm (ATSDR, 2000). ACGIH (1992) has summarized the acute toxicity thresholds for toluene as follows. Inhalation of 100 to 200 ppm (375 to 750 mg/m^3) is associated with headaches and mild transient irritation of the upper respiratory tract; 400 ppm (1,500 mg/m^3) is associated with eye irritation, lacrimation and giddiness; 600 ppm (2,250 mg/m^3) with lethargy, giddiness and slight nausea; 800 ppm (3,000 mg/m^3) is associated with moderate to severe eye and upper respiratory tract irritation, drowsiness, nasal discharge, ataxia, dizziness and metallic taste in the mouth. In a review of the available occupational studies, ACGIH (1992) concluded that the highest toluene air concentrations that can be tolerated for short durations (3.5 to 6 hours) without measurable neurobehavioural effects were 80 to 100 ppm (300 to 375 mg/m^3).

Using toxicokinetic models to extrapolate an air concentration from a blood concentration, Hobara *et al.* (2000) estimated that a toluene air concentration of 1,800 to 2,000 ppm (6,750 to 7,500 mg/m^3) for one hour was fatal to a painting worker who died following high intensity exposure to paint thinner. Cardiac arrhythmias were noted in two adult males who were found semi-conscious after suffering from severe toluene intoxication (>7,000 mg/m^3 toluene) while removing glue from tiles in a swimming pool (Meulenbelt *et al.*, 1990). Responses were variable between these individuals. One man, exposed for two hours, exhibited a rapid heartbeat (sinus tachycardia), while the second man, exposed for three hours, had a slowed heartbeat (bradycardia). Severe sinus bradycardia was reported in a comatose man with severe toluene intoxication who had sniffed approximately 250 mL of thinner containing more than 50% toluene (Einav *et al.*, 1997).

Irritation of the nose and throat was reported in human volunteers exposed to 200 ppm (750 mg/m^3) toluene for seven to eight hours (Carpenter *et al.*, 1944).

Echeverria *et al.* (1989) exposed 42 college students (21 females and 21 males) to 0, 74 ppm (279 mg/m^3) or 151 ppm (569 mg/m^3) toluene for seven hours over a three day period. This exposure sequence was repeated for a total of 42 exposures over a three month period. The odour of toluene was masked in this study. Test results for visual perception differed from control values in both exposed groups. Results of a manual dexterity test differed from control values in the high, but not the low exposure group. Psychomotor test results were similar in all groups. Subjective symptoms increased with increasing exposure level and were characterized by complaints of eye irritation, headache and somnolence. A no-observable-adverse-effect-level (NOAEL) of 74 ppm was identified from this study. The duration-adjusted NOAEL was reported to be 32 ppm (122 mg/m^3) (U.S. EPA, 1992).

Andersen *et al.* (1983) exposed 16 subjects (average age of 24 years) to 0, 10, 40 or 100 ppm (0, 38, 151 or 377 mg/m^3) toluene for six hours over four consecutive days. At 100 ppm, irritation was experienced in the eyes and nose, but no effect on nasal mucous flow or lung function was observed. These subjects frequently reported headaches, dizziness and a feeling of intoxication. Such effects were not reported in the 10 or 40 ppm groups. No effects were observed in performance tests, although subjects did report that it became increasingly difficult to conduct psychometric tests and that their reaction times felt impaired at 100 ppm toluene. This study indicates lowest-observable-adverse-effect-level (LOAEL) of 100 ppm and a NOAEL of 40 ppm.

von Oettingen *et al.* (1942) exposed three human volunteers to toluene air concentrations ranging from 50 to 800 ppm (188 to 3,000 mg/m^3) of toluene for eight hours a day, two times per week for eight weeks. At 200 ppm (750 mg/m^3), volunteers experienced muscle weakness, confusion, impaired coordination and dilated pupils. Post-exposure effects included fatigue, general confusion and moderate insomnia. One subject exposed to 100 ppm (375 mg/m^3) complained of moderate fatigue, sleepiness and headaches. At 200 to 800 ppm, symptoms of muscle weakness, confusion, lightheadedness, impaired coordination, paraesthesia and nausea were reported. As the duration increased, narcosis, and impaired intellectual, psychomotor and neuromuscular effects were reported. After exposure to 800 ppm, all three subjects reported considerable after effects (severe nervousness, muscular fatigue and insomnia), which lasted several days. No effects on systolic or diastolic blood pressure, or pulse rate were reported in volunteers exposed to 800 ppm toluene for three hours.

Wilson (1943) reported a series of subjective symptoms (headaches, lethargy and loss of appetite) in workers that had been exposed to toluene air concentrations ranging from 50 to 200 ppm (188 to 750 mg/m^3) for periods of one to three weeks. At 200 to 500 ppm (750 to 1,875 mg/m^3), workers experienced nausea, a bad taste in the mouth, slightly impaired coordination and reaction time, and temporary memory loss. Exposure to 500 to 1,500 ppm (1,875 to 5,600 mg/m^3) led to palpitations, extreme weakness, pronounced loss of coordination, and impaired reaction time.

Ogata *et al.* (1970) reported delayed hand-eye reaction times in volunteers inhaling 200 ppm (750 mg/m^3) toluene for seven hours. However, hand-eye reaction times were found to be increased in male human volunteers exposed to more than 300 ppm (1,125 mg/m^3) in four 20-minute exposures (Gamberale and Hultengren, 1972). Perceptual speed was noted to be impaired in these subjects at 700 ppm (2,625 mg/m^3). No effects were observed at 100 ppm (375 mg/m^3).

Dick *et al.* (1984) found that visual vigilance task performance was impaired within the first two hours of a four-hour exposure of human volunteers to 100 ppm (375 mg/m^3) toluene. Olson *et al.* (1985) found no effects on reaction time, or memory reproduction in volunteers inhaling 80 ppm (300 mg/m^3) toluene for four hours.

Baelum *et al.* (1985) reported that two groups of workers (one with previous occupational exposure to solvents and one without), exposed once to 100 ppm (375 mg/m^3) of toluene for 6.5 hours, displayed such symptoms as fatigue, drowsiness, a sense of inebriation, and eye, nose and throat irritation. Workers also displayed reduced manual dexterity, a reduced ability to discriminate colours, and deteriorated visual perception. The group that was previously exposed to solvents was noted to appear to have a greater sensitivity to toluene. The authors concluded that little tolerance develops to the irritative and CNS effects of toluene in humans.

Rahill *et al.* (1996) reported that six human volunteers exposed to 100 ppm (375 mg/m^3) toluene for six hours, followed by exercise, showed significantly lower results on neuropsychological tests than volunteers exposed to clean air.

Ten paint-sprayers exposed to a solvent mixture (containing 0.8 to 4.8 ppm toluene; 3 to 18 mg/m^3) and dusts showed morphological changes in the nasal mucosa (Hellquist *et al.*, 1983). Forty-two workers exposed to mixtures of solvents, of which toluene was known to be a major component, reported symptoms of nasal irritation, in addition to eye irritation, nausea, skin conditions, dizziness, and headaches (Winchester and Madjar, 1986). The air concentrations of toluene in this study ranged from 1 to 80 ppm (3.75 to 300 mg/m^3) with a mean of 15 ppm (56 mg/m^3). However, concurrent exposure to a mixture of solvents and dusts in both these studies precludes establishing a reliable causal relationship between toluene exposure to toluene and nasal mucosa irritation.

Neubert *et al.* (2001) conducted a controlled, multi-center, blinded field trial to investigate effects associated with acute toluene exposure in workers of 12 German rotogravure factories. Medical examinations (including questions on subjective symptoms, and standard tests of psycho-physiological and psycho-motor functions) were performed on roughly 1,500 volunteers, of whom 1,290 were toluene-exposed (1,178 men and 112 women). There were 194 referents (157 men and 37 women). All volunteers worked the morning shift (six hour exposure). Convincing dose-dependent acute effects could not be demonstrated with regression analyses or group statistics in male volunteers at the exposure levels evaluated. It was concluded that ambient air concentrations (time-weighted average over six hours) between 50 and 100 ppm (188 to 375 mg/m^3) were not convincingly associated with alterations in psycho-physiological and psycho-motor performances, or an increased frequency of subjective complaints in male volunteers.

In laboratory animals, acute exposure to toluene has both excitatory and depressant effects on the CNS, with numerous animal studies clearly indicating a biphasic response showing low-concentration stimulation and high-concentration depression of motor activity (ATSDR, 2000). Other effects reported in experimental animals exposed to toluene *via* inhalation for acute exposure durations include: various manifestations of neurological and neurobehavioural effects, altered heart rate and rhythm, hematological effects, impaired disease resistance, altered enzyme and neurotransmitter levels, body and organ weight changes, and impaired auditory function.

The one-hour LC_{50} for toluene in the rat is 26,700 ppm (100,000 mg/m^3) (Pryor *et al*, 1978). The six-hour LC_{50}s in rats and mice are 4,618 ppm (17,320 mg/m^3) and 6,949 ppm (26,060 mg/m^3), respectively (Bonnet *et al*., 1982). An eight-hour LC_{50} of 5,300 ppm (19,900 mg/m^3) is reported for the mouse (Svirbely *et al*, 1943). An inhalation LC_{50} of 40,000 ppm was reported for rabbits exposed to toluene for 2.3 hours (Carpenter *et al*., 1944).

In dogs killed by rebreathing one litre of air containing 30,000 ppm (112,500 mg/m^3) toluene *via* an endotracheal tube, the cause of death was due to hypoxia in most cases, but four dogs developed transient arrhythmia and in one case, death occurred from ventricular fibrillation before fatal hypoxia could occur (Ikeda *et al*., 1990). In rats, inhalation of 66,276 ppm (248,535 mg/m^3) toluene for 35 minutes was fatal to all animals, and produced increased heart rate and changes in electrocardiographs indicative of depressed ventricular conduction, prior to death (Vidrio *et al*., 1986).

Daily exposure of neonate rats to 10,000, 20,000 or 40,000 ppm (37,500, 75,000 or 150,000 mg/m^3) toluene for 15 minutes from postpartum days 2 to 30 produced a concentration-related increase in the time taken for the righting-reflex to occur (Lorenzana-Jimenez and Salas, 1990). At each concentration tested, the time taken for the righting-reflex to occur decreased over the first four weeks of exposure, then increased over the last four weeks of exposure, but never regained the latency observed in the first week of the study. The authors suggest that rats may be able to develop tolerance to the acute neurobehavioral effects of toluene.

In male rats exposed to 2,000 ppm (7,500 mg/m^3) toluene for 48 hours, increased hematocrit and blood glucose levels were observed (Tahti *et al*., 1983). Male rats also had increased serum levels of alanine aminotransferase and aspartate aminotransferase. Body weights were decreased relative to controls.

Aranyi *et al*. (1985) conducted a study of immune response following toluene exposure. Mice were exposed for three hours per day, for five days per week or for four weeks to 1.0 to 500 ppm (3.75 to 1,875 mg/m^3) toluene and then challenged by *Streptococcus zooepidemicus*. It was found that at concentrations >100 ppm (375 mg/m^3), there was decreased resistance to respiratory infection. Exposure to 1 ppm caused no significant difference in susceptibility relative to controls. Pulmonary bactericidal activity was decreased at concentrations of 2.5 ppm (9.4 mg/m^3) and 100 to 500 ppm, but not at all concentrations in the 5 to 50 ppm (19 to 188 mg/m^3) range. The bactericidal activity of the lung was decreased during the five-day treatment but not the four week treatment. The authors suggest that toluene exerted an adverse effect on alveolar macrophage function, which decreased disease resistance.

Rats exposed to 4,000 ppm (15,000 mg/m^3) toluene for six hours showed a significant increase in hepatic levels of cytochrome P450 (CYP) 2E1, increased hepatic activities of nitrosodimethylamine demethylase and 7-pentoxyresorufin O-depentylase and decreased levels of CYP2C11 (Wang *et al.*, 1996).

Attention deficits and impaired visual-motor abilities were observed in six macaque monkeys exposed by inhalation for 50 minutes to 2,000 to 4,500 ppm (7,500 to 17,000 mg/m^3) toluene (Taylor and Evans, 1985). The authors also noted that expired carbon dioxide increased in a dose-dependent manner from 100 to 3,000 ppm (375 to 11,000 mg/m^3). The investigators state that changes in expired carbon dioxide may provide evidence of combined behavioural, respiratory, sensory, and metabolic effects.

Dose-dependent decreases in behavioural performance and CNS depression were observed in mice and rats exposed by inhalation to toluene at concentrations ranging from 2,600 to 12,000 ppm (9,800 to 45,000 mg/m^3) for up to three hours (Bruckner and Peterson, 1981). Younger animals were more susceptible to toluene toxicity, and mice were more sensitive than rats.

Kishi *et al.* (1988) reported that exposure of rats to 125, 250 or 500 ppm (469, 938 or 1,875 mg/m^3) toluene for four hours produced a decline in lever-press shock avoidance performance 20 minutes after exposure began. Recovery was complete by two hours post-exposure. Previously, Wood *et al.* (1983) found that exposure to greater than 480 ppm (1,800 mg/m^3) toluene for four hours decreased the ability of trained rats to perform a sequence of lever press actions associated with a reward.

Ikeda *et al.* (1986) reported significant localized changes in dopamine (DA) or norepinephrine (NE) brain levels in rats exposed to 400 ppm (1,500 mg/m^3) toluene 24 hours a day for 30 days. von Euler *et al.* (1989) found that newborn male rats had significant localized changes in dopamine DA or NE brain levels seven weeks after a 10 day exposure to 80 ppm (300 mg/m^3) toluene for six hours per day. A concentration of 80 ppm was also found to affect dopamine D2 agonist binding in the rat caudate-putamen (Hillefors-Berglund *et al.*, 1995; von Euler *et al.*, 1993). Dopamine levels were increased in the cerebellum and striatum of rats exposed to 1,000 to 4,000 ppm (3,750 to 15,000 mg/m^3) toluene for 20 minutes, while NE and 5-hydroxytryptamine were significantly increased in the cerebellum and cortex (Kim *et al.*, 1998).

Significant changes in the activities of enzymes responsible for neurotransmitter synthesis (glutamic acid decarboxylase, choline acetyltransferase and aromatic amino acid decarboxylase) were observed in male rats exposed to 50 to 1,000 ppm (188 to 3,750 mg/m^3) toluene for four weeks or 500 ppm (1,875 mg/m^3) for 12 weeks (Bjornaes and Naalsund, 1988).

von Euler *et al.* (2000) investigated the effect of an inhalation exposure of 80 ppm (300 mg/m^3) for four weeks, at six hours per day, five days per week in rats. Rats were observed after a post-exposure period of at least four weeks. Toluene exposure at 80 ppm appeared to adversely affect spatial memory (based on Morris swim maze performance) and also resulted in increased locomotion and rearing behaviours and a significantly reduced beam-walk performance. Upon necropsy, the area of the cerebral cortex, especially the parietal cortex, was found to be decreased by 6 to 10% in the exposed rats.

Wiaderna and Tomas (2002) exposed male rats to 25, 100 and 250 ppm (94, 375 and 938 mg/m^3) toluene for six hours per day, five days per week for four weeks. The following behaviours were tested: finding water in a radial maze; open field motor activity, acquiring the conditional response of passive avoidance; sensitivity to a thermal pain stimulus (hot plate test) and changes in this sensitivity caused by stress; and acquiring the conditional response of two-directional active avoidance. In addition, behavioural response to apomorphine (*i.e.*, increased spontaneous locomotor activity), was assessed on post-exposure day 10. In the behavioural experiments, significant differences between groups were only observed for the hot plate test. In the 100 and 250 ppm groups, electric-shock-related anxiety responses were stronger, relative to controls. The behavioural response to apomorphine in the 100 ppm or 250 ppm groups was significantly lower than in controls.

Rats continuously exposed to toluene at 320 ppm (1,200 mg/m^3) for 30 days had decreased total brain weight and decreased weight of the cerebral cortex (Kyrklund *et al.*, 1987). There was also a decrease in the total phospholipid content of the cerebral cortex which was accompanied by a small increase in phosphatidic acid levels.

Harabuchi *et al.* (1993) found that rats exposed to 4,000 ppm (15,000 mg/m^3) toluene for four hours during daylight demonstrated poorer shock avoidance than animals exposed during the dark. A correlation was noted between shock avoidance behaviour and toluene levels in the brain, with higher brain toluene levels associated with reduced ability to press the lever that prevents electrical shock.

Single four or eight hour exposures to toluene in the concentration range of 900 to 4,000 ppm (3,375 to 15,000 mg/m^3) and repeated exposures to 900 or 2,700 ppm (3,375 or 10,125 mg/m^3) for eight hour per day for three weeks, were found to alter sleep and wakefulness patterns in rats (Arito *et al.* ,1988; Takeuchi and Hisanaga, 1977).

Miyagawa *et al.* (1998) reported that rats exposed to 1,600 or 3,200 ppm (6,000 or 12,000 mg/m^3) toluene for four hours showed a concentration-related decrease in accuracy in a neurological test of short-term memory function.

Johnson and Canlon (1994) found that a loss of outer hair cells in the cochleae of rats occurred following exposure to 1,400 ppm (5,250 mg/m^3) toluene for 14 hours per day, for eight days. Outer hair cell loss was first observed by day five of exposure, and this loss had progressed to the inner hair cells at six weeks post-exposure.

McWilliams *et al.* (2000) found that temporary disruption of auditory function occurred in guinea pigs exposed to 250, 500 and 1,000 ppm (938, 1,875 and 3,750 mg/m^3) toluene for eight hours a day, five day per week for one and four weeks. Concentrations as low as 250 ppm toluene disrupted auditory function acutely in the guinea pig, and 500 and 1,000 ppm toluene produced a greater degree of acute auditory dysfunction.

Lataye *et al.* (2003) reported that rats exposed to 600 ppm (2,250 mg/m^3) toluene for six hour a day for five days showed severe disruption of auditory function and cochlear pathology while similarly exposed guinea pigs displayed no adverse auditory effects.

Tables 6 and 7 provide summaries of relevant acute human and experimental animal inhalation toxicity studies with toluene.

Table 6 Summary of Acute Human Toxicity Studies with Toluene

Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
7 to 8 hours	750	Irritation of nose and throat	Carpenter *et al.*, 1944
6 hours over 4 d	375	Headaches, dizziness irritation of eyes and nose	Andersen *et al.*, 1983
7 hours over 3 d	569	Decrements in visual short term memory, visual perception and psychomotor skills	Echeverria *et al.*, 1989
8 h/d, 2 times/wk for 8 wks	750	Muscular weakness, confusion, impaired coordination, dilated pupils	von Oettingen *et al.*, 1942
7 h	750	Delayed hand-eye reaction time	Ogata *et al.*, 1970
20-minute	1,000	Impaired reaction time	Gamberale and Hultengren, 1972
6.5 hours	375	Fatigue, sleepiness, inebriation, eye, nose and throat irritation, reduced psychometric performance	Baelum *et al.* 1985
6 hours	375	Lower results on neuropsychological tests	Rahill *et al.*, 1996

Table 7 Summary of Acute Inhalation Studies with Toluene in Experimental Animals

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
Rats (neonate)	15 minutes from postpartum d 2 to 30	>37,500	Concentration-related increase in time for right tightening-reflex	Lorenzana-Jimenez and Salas, 1990
Rats (male)	48 hours	7,500	Increased hematocrit and blood glucose levels	Tahti *et al.*, 1983
Rats	6 hours	15,000	Biochemical effects	Wang *et al.*, 1996
Macaque monkeys	50 minutes	7,500 to 17,000	Attention deficits and impaired visual-motor abilities	Taylor and Evans, 1985
Mice	up to 3 hours	9,800 to 45,000	Behavioural effects and CNS depression	Bruckner and Peterson, 1981
Rats	up to 3 hours	9,800 to 45,000	Behavioural effects and CNS depression	Bruckner and Peterson, 1981

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
Rats	4 hours	>469	Reversible behavioural effects 20 minutes following beginning of exposure	Kishi *et al.*, 1988
Rats	24 h/d for 30 d	1,500	Biochemical effects	Ikeda *et al.*, 1986
Rats (newborn males)	6 h/d for 10 d	300	Biochemical effects	von Euler *et al.*, 1989
Rats	20 minutes	3,750 to 15,000	Biochemical effects	Kim *et al.*, 1998
Rats (male)	4 weeks	188 to 375	Biochemical effects	Bjornaes and Naalsund, 1988
Rats (male)	6 h/d, 5 d/wk for 4 wks	375	Behavioural effects	Wiaderna and Tomas, 2002
Rats	30 days	1,200	Decreased total brain weight and weight of cerebral cortex	Kyrklund *et al.*, 1987
Rats	4 hours	6,000 and 12,000	Concentration-related decrease in accuracy of short-term memory	Miyagawa *et al.*, 1998
Rats	14 h/d for 8 d	5,250	Loss of outer hair cells in cochlea	Johnson and Canlon, 1994
Guinea pig	8 h/d, 5 d/wk for 1 and 4 wks	938	Disrupted auditory function	McWilliams *et al.*, 2000
Guinea pig	6 h/d for 5 d	2,250	No auditory effects	Lataye *et al.*, 2003
Rats	6 h/d for 5 d	2,250	Disruption of auditory function and cochlear pathology	Lataye *et al.*, 2003

4.1.3 Subchronic and Chronic Toxicity

It is well established that neurotoxicity and neurobehavioural deficits are the principal effects of long term inhalation exposure to toluene in both humans and experimental animals. The major symptoms following subchronic or chronic inhalation exposure to toluene in humans include subtle changes in neurological functions including cognitive and neuromuscular performance, hearing and colour discrimination in chronically exposed workers. Subchronic or chronic studies with experimental animals also indicate that major symptoms of toluene exposure include behavioural changes, hearing loss, and subtle changes in brain structure, brain electrophysiology, and brain chemistry.

Studies of occupationally exposed workers also indicate that chronic exposure to toluene concentrations ranging from 30 to 130 ppm (113 to 488 mg/m^3) can lead to deficits in hearing and colour vision. Hearing loss has also been reported in experimental animals exposed to 700 to 1,500 ppm (2,625 to 5,625 mg/m^3) toluene (ATSDR, 2000).

There are numerous case reports of solvent abusers who repeatedly inhaled high concentrations of toluene vapours. The kidney appears to be a target organ in individuals that abuse solvents containing toluene. The types of effects reported in these individuals include: severe renal tubular acidosis (Goodwin, 1988); severe tubular interstitial nephritis and focal tubular necrosis (Taverner *et al.*, 1988); acidosis and hypokalemia (Gerkin and LoVecchio, 1998); proteinuria, hematuria, urinary calculi, severe renal tubular degeneration and necrosis, massive bilateral adrenal hemorrhage with severe degeneration and necrosis of the adrenal cortex (Kamijo *et al.*, 1998). It is also common in case reports of chronic solvent abusers to see evidence of severe and often permanent neurological damage such as abnormal electroencephalogram (EEG) activity, ataxia, tremors, temporal lobe epilepsy, paranoid psychosis, hallucinations, nystagmus (involuntary eye movement), cerebral atrophy, and impaired speech, hearing, and vision, and reduced intelligence (ATSDR, 2000).

The findings from case studies of chronic toluene abusers suggest that some neurological symptoms may stem from permanent structural changes in the brain, including an increase in the white matter signal, a loss of gray and white matter differentiation, and decreased perfusion in the cerebral cortex, basal ganglia, and thalami, as well as cerebral, cerebellar, and brainstem atrophy, abnormalities in MRI and brainstem auditory evoked response (BAER) (ATSDR, 2000). However, symptoms observed in individuals engaged in intentional and severe solvent abuse are not typical of ambient exposure conditions. Thus, further discussion of effects seen in solvent abusers is not relevant to the development of an ambient air quality objective for toluene. The reader is referred to the ATSDR (2000) report on toluene for a more detailed discussion on health effects as they relate to chronic solvent abuse.

A large number of human occupational epidemiology studies have been conducted that investigated workers exposed to toluene in air for chronic durations. However, all available studies suffer from a number of limitations including small cohort or sample sizes, co-exposure to multiple solvents, and a lack of adequate historical exposure monitoring data. Selected relevant studies are summarized in the following paragraphs.

Foo *et al.* (1990) conducted a cross-sectional study of 30 female workers employed at an electronic assembly plant where toluene was a component of glue. Toluene levels reported in this study were obtained from personal samplers and were reported as eight-hour time weighted averages; however, no information was provided on the number of samples or the duration of the sampling period. Exposed and control groups were matched for age, ethnicity, and use of medications. Study subjects were reported to be non-drinkers and non-smokers, and had no prior medical history of central or peripheral nervous system disorders. The average number of years worked was 5.7 years for the exposed population and 2.5 years for the control group. Personal sampler data for the exposed group indicated average toluene air concentrations of 88 ppm (332 mg/m^3). The control group was exposed to lower average toluene air concentrations (13 ppm; 49 mg/m^3). A battery of eight neurobehavioural tests were administered to all exposed and control workers. There were statistically significant differences between the exposed and control groups in six out of eight tests, with all tests showing that exposed workers performed poorly relative to controls. However, there was a weak correlation between test responses and toluene air concentrations. The authors identified a LOAEL of 88 ppm toluene (332 mg/m^3) for neurobehavioral changes. Although the study did not focus on irritation effects, no clinical signs or symptoms of irritation were reported. This study is limited by incomplete exposure information, the small sample size, apparent lack of an exposure-response relationship, the fact that controls were not "true" controls (*i.e.*, the control group was exposed to an average of

13 ppm toluene, and failure to account for potential co-exposure to other solvents in the workplace.

Another group of 29 exposed electronics workers in Singapore was found to perform worse than a control group based on eight neurobehavioral tests. The average time-weighted average (TWA) toluene exposure was 90.9 ppm (341 mg/m^3) in the exposed group and 12.2 ppm (46 mg/m^3) in the control group. The exposed group also performed significantly worse in verbal and nonverbal memory test as measured by the digit span and visual reproduction tests (Boey *et al.*, 1997). As for the Foo *et al.* (1990) study, controls were not "true" controls (*i.e.*, the control group was exposed to an average of 12.2 ppm toluene). This limits interpretation of the study findings.

Hanninen *et al.* (1987) conducted a battery of 11 psychological tests on 43 printing workers who were occupationally exposed to approximately 117 ppm (441 mg/m^3) toluene for an average of 22 years. Only mild adverse effects were observed in 2 of 11 tests. However, the control and exposed cohorts in this study were mismatched in several areas, including alcohol use (U.S. EPA, 1992). In a similar study, Iregren (1982) examined the psychological performance of 38 printers who were occupationally exposed to 50 to 150 ppm (188 to 565 mg/m^3) toluene for an average of 16.3 years. No adverse effects were reported. However, the cohorts evaluated in this study were apparently matched only by age (U.S. EPA, 1992). In another study of printing workers, Cherry *et al.* (1985) attempted to better match the control and exposed cohorts and account for alcohol use. A total of 52 workers were studied. Workplace toluene concentrations reportedly ranged up to >500 ppm (1,875 mg/m^3). No significant differences were found between the two cohorts, but exposed workers performed worse than the controls on 10 of 13 psychological tests.

Lee *et al.* (1988) conducted a study of 193 female workers (and 65 controls). Both groups completed a questionnaire that listed 67 symptoms. Toluene exposures were reported as eight-hour TWAs, and workers were grouped in the following categories: non-exposed controls, 1 to 50 ppm (3.75 to 188 mg/m^3), 51 to 100 ppm (191 to 375 mg/m^3), 101 to 150 ppm (379 to 563 mg/m^3), and >151 ppm (566 mg/m^3). Exposure durations were not reported. A concentration-dependent increase in prevalence was reported for 25 of 67 symptoms on the questionnaire with increases in complaints (relative to controls) occurring at around 100 ppm (375 mg/m^3). The complaints at this concentration included headaches, sore throats, and dizziness. While this study suggests an effect level of around 100 ppm, it is based on subjective self-reporting of symptoms, rather than objective measures of toxicity.

Tahti *et al.* (1981) reported that workers exposed for several years to toluene in a tarpaulin factory had increased blood leukocyte counts. Toluene air concentrations ranged from 20 to 200 ppm (75 to 750 mg/m^3). However, there was co-exposure to benzene in this factory with benzene concentrations reported to be less than 10 ppm. Thus, this study is of limited value as the findings appear to be confounded by benzene co-exposure (leukocytes are a known target cell type of benzene). Other limitations of this study include a small cohort size and a lack of historical exposure monitoring (ATSDR, 2000).

Hematological effects were also reported in Stengel *et al.* (1998). This study found that blood immunoglobulin E (IgE) levels were significantly elevated (relative to controls) in 92 printers exposed to 97 to 232 mg/m^3 of toluene for an average of 16 years. A dose-response relation was observed for cumulative toluene exposure and IgE levels.

In a cross-sectional study, Guzelian *et al.* (1988) reported that eight men employed at a printing factory that were exposed to <200 ppm (750 mg/m^3) toluene, exceeded the upper end of the normal range for blood levels of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase, (AST), and alkaline phosphatase (AP), and had an ALT/AST ratio greater than one. In addition, liver biopsies showed centrilobular and periportal fat accumulation and Kupffer cell hyperplasia. None of these subjects had reported drinking alcohol to excess, but they may have had minor occupational exposure to methyl alcohol, ethyl alcohol, diethyl ether, trichloroethylene, and lacquer thinners which may have confounded these results. The subjects had returned to work after a four-day vacation. Within the first two days, they reported a feeling of mild intoxication to which they became tolerant after two days.

An early study of 106 painters exposed to toluene at an airplane factory reported enlarged liver in 30.2% of the exposed men, versus 7% in controls (Greenburg *et al.*, 1942). However, results of this study are unreliable as pre-1950s, occupational exposure to toluene was associated with exposure to benzene, which was a common contaminant of toluene mixtures at that time.

Tests of postural sway were conducted on 27 United States Air Force workers exposed to jet fuel (a mean cumulative exposure to toluene of 23.8 ± 6.1 ppm (or 89 ± 23 mg/m^3) was estimated) (Smith *et al.*, 1997). A significant association between toluene exposure and increased postural sway was reported. However, the results of this study are confounded by concurrent exposure to other chemicals, including benzene, xylenes, and various other aliphatic and aromatic hydrocarbons present in jet fuel vapour.

Orbaek and Nise (1989) examined the neurological effects of toluene exposure on 30 rotogravure printers, 33 to 61 years of age (mean age = 50), that were employed at two Swedish printing shops for 4 to 43 years (median= 29) in 1985. The mean toluene air concentrations at the two shops were 43 and 157 mg/m^3 respectively. Prior to 1980, toluene air concentrations frequently exceeded 300 mg/m^3 in both shops. The authors noted that the rotogravure printing process uses high purity toluene. Comparisons were made to a reference group of 72 men aged 27 to 69 years (mean=47 years). Neurological function in the workers and referents was evaluated using interviews and psychometric testing. The data from both shops were pooled. Printers reported significantly higher occurrences of fatigue (60%), short-term memory problems (60%), concentration difficulties (40%), mood lability (27%), and other neurasthenic symptoms, relative to controls. The printers also scored significantly worse than referents in a number of psychometric tests, even after adjustment for age. Alcohol consumption was also evaluated as a variable in this study and for all comparisons performed, interaction between the effects of toluene exposure and alcohol consumption were not statistically significant.

Murata *et al.* (1993) compared cardiac autonomic function in printers exposed to 83 ppm (311 mg/m^3) toluene for 1 to 36 years with matched un-exposed controls. Autonomic function was evaluated based on measurements of heart rate, the coefficient of variation in electrocardiographic R-R intervals, the distribution of nerve conduction velocities, and the maximal motor and sensory nerve conduction velocities in the median nerve. Some exposed printers reported subjective symptoms such as fatigue, headache and irritation. Heart rate was found to not significantly differ between the exposed and control groups. Statistically significant reductions in electrocardiographic R-R intervals were observed in the exposed group, which the authors considered indicative of possible dysfunction of the autonomic nervous system. There was also a significant decrease in the motor and sensory conduction velocity in the palm segment of the median nerve in exposed workers, but there was no significant difference in the distribution of the nerve conductance velocities between the exposed and control groups.

In a study by Yin *et al.* (1987), 94 solvent workers (38 men and 56 women with average employment duration of 6.8 years) and 138 controls (48 men and 90 women) were evaluated using diffusion dosimeters, questionnaire, hematology and urinalysis. The mean toluene air concentration (expressed as a seven hour mean TWA) was estimated at 42.8 ppm (161 mg/m^3). The maximum estimated air concentration was 123 ppm (464 mg/m^3). Workers were also co-exposed to 1.3 ppm benzene. No exposure-related effects were noted in any of the biochemical parameters examined. The prevalence of subjective symptoms was significantly higher in the exposed workers relative to controls, but a concentration-response relationship could not be established. No other treatment-related effects were reported. The study was limited because the exposed and unexposed groups were not matched to control for confounding effects (*e.g.*, age, smoking, alcohol consumption, exposure duration) and neither respiratory irritation nor psychological performance was directly evaluated in the exposed workers (U.S. EPA, 1992).

Abbate *et al.* (1993) evaluated auditory alterations in a group of rotogravure workers exposed to toluene. A sample of 40 workers of normal hearing ability was selected from a group of 300 workers who were outwardly healthy and were occupationally exposed to toluene for 12 to 14 years. The average toluene air concentration was reported to be 97 ppm (364 mg/m^3). An age and sex-matched control group was also evaluated. The subjects underwent an adaptation test utilizing a brainstem auditory evoked response (BAER) technique with 11 and 90 stimulus repetitions a second. A statistically significant alteration in the BAER results was observed in the exposed workers at both 11 and 90 stimuli repetitions. There were no clinical signs of neuropathy reported.

Morata *et al.* (1997) conducted a cross-sectional study of 124 Brazilian workers exposed to various levels of noise and a variety of organic solvents, including toluene at TWA concentrations ranging from 0.037 to 244 ppm (median=122 ppm; 458 mg/m^3). Toluene concentrations were estimated by personal monitoring and measurement of hippuric acid in urine. It was found that roughly half of exposed workers experienced hearing loss. Logistic regression analysis showed hippuric acid concentration to be significantly associated with hearing loss and the odds ratio estimates for hearing loss were 1.76 times greater for each gram of hippuric acid per gram creatinine in urine. However, confidence in the study is limited due to co-exposure to multiple solvents and possible confounding effects from noise exposure.

Schaper *et al.* (2003) investigated the ototoxicity of occupational exposure to toluene at concentrations below 50 ppm (188 mg/m^3) in a five-year longitudinal study. There were four repeated examinations of 333 male workers from rotogravure printing plants. Past lifetime weighted average exposures (LWAE) to toluene and noise were determined from individual work histories, and recent individual exposures were measured 10 times during the study. The mean LWAE exposures to toluene and noise were 45±17 ppm plus 82±7 dB(A) for printers (high toluene intensity group) and 10±7 ppm plus 82±4 dB(A) for end-processors (low toluene intensity group). The mean current exposures to toluene and noise during the study were 26±20 ppm plus 81±4 dB(A) for printers, and 3±3 ppm plus 82±4 dB(A) for the end-processors. The study found no significant effects of toluene intensity, of exposure duration and of interactions between toluene intensity and noise intensity on auditory function. The authors concluded that the threshold level for developing a hearing loss as a result of occupational toluene exposure appears to be above 50 ppm (188 mg/m^3).

Occupational exposure to toluene may also affect other sensory-evoked potentials. Vrca *et al.* (1997) studied a group of 49 printing-press workers who were occupationally exposed to toluene for approximately 21.6 years. Toluene exposure was determined from blood toluene and urinary hippuric acid levels, and was estimated to range from 40 to 60 ppm (150 to 225 mg/m^3). Brain evoked auditory potential (BEAP) and visual evoked potential (VEP) measurements were performed on a Monday morning after workers had the weekend off. A significant increase was noted in the latencies of BEAP waves examined, except for P2 waves, as well as in the interpeak latency (IPL) P3-P4. IPL P4-P5 decreased significantly with the length of exposure. No correlation was observed between the amplitude of BEAP waves and the length of exposure. The amplitude, but not the latency, of all the VEPs examined decreased significantly with the length of exposure. This particular study is limited by the lack of a control group for comparisons. However, previous studies of this group of workers did utilize controls (matched for alcohol and coffee consumption, smoking, age, years of work, education and head injuries) (Vrca *et al.*, 1995). Toluene exposure was estimated in the same manner. The amplitudes of the N75, P100 and N145 waves, and the latency of the P100 wave, were significantly increased in exposed subjects relative to controls. BAEPs showed a significant decrease in all wave amplitudes and a significant increase in all wave latencies except P2.

Chronic occupational exposure to toluene has also been associated with impaired colour vision. Zavalic *et al.* (1998a) examined colour vision in 83 controls, 41 shoemakers and 32 printers exposed respectively to geometric mean toluene air concentrations of 0, 35 or 156 ppm (0, 131 or 585 mg/m^3). Toluene exposure was estimated by measuring toluene levels in air, blood, and by measuring the amount of hippuric acid and orthocresol in urine at the end of the work shift. It was found that colour confusion was significantly higher in printers, relative to both shoemakers and controls. Colour confusion index was increased in shoemakers relative to controls but was not statistically significant. Regression analysis indicated a significant correlation between colour confusion and alcohol intake and age in the controls. Age- and alcohol-adjusted colour confusion index was significantly increased in printers relative to both shoemakers and controls, and in shoemakers compared with controls. After age and alcohol adjustments, it was found that individual colour confusion indices were significantly correlated with individual exposure estimates (based on air, blood, or urine measurements) in printers, but not in shoemakers.

Colour vision impairment was also evaluated in another group of 45 male workers exposed to mean concentrations of 120 ppm (450 mg/m^3) toluene (Zavalic *et al.*, 1998b). It was reported that colour vision was significantly impaired in exposed workers compared with un-exposed controls. A comparison of colour vision assessments made on Monday and Wednesday mornings showed no significant difference, which lead the authors to suggest that colour vision impairment results from chronic rather than acute toluene exposure.

Zavalic *et al.* (1998c) conducted further analysis of colour vision loss in the same groups of workers evaluated in Zavalic *et al.* (1998a). This study focused on loss in the blue-yellow and red-green ranges. It was found that both blue-yellow and red-green colour confusion were significantly increased in printers, but there was no significant difference in the prevalence of either type of colour confusion between the exposed and unexposed workers.

Muttray *et al.* (1995; 1999) also studied toluene's effects on vision in occupational settings. The 1995 study assessed colour vision in 59 male rotogravure workers occupationally exposed to unspecified levels of toluene for periods of 1 month to 36 years (mean =10 years). No vision testing was conducted at the beginning and end of the work week. No differences were noted in this study. The 1999 study compared colour vision in eight occupationally exposed printers and eight workers previously unexposed to toluene, before and after cleaning of a print machine with toluene. This task comprised 28 to 41 minutes and involved exposure to 300 to 362 ppm toluene (1,125 to 1,358 mg/m^3). No impairment in colour vision was observed. However, a comparison of the pre-cleaning colour vision performance of the printers with that of a group of matched controls showed a non-significant decrease in colour vision for the printers. It was suggested that this might indicate a chronic effect of toluene exposure on colour vision (Muttray *et al.*, 1999). In an earlier study, Muttray *et al.* (1997) found that workers exposed to mixed solvents (including toluene) during a spraying process showed a significant impairment of colour vision, characterized by errors of the blue-yellow type.

In a recent review of the available studies on chemical exposure (including toluene) and effects on colour vision, Iregren *et al.* (2002) noted that while colour vision seems to be a physiological function that is very sensitive to several chemicals, toluene effects are not well established, as many studies have found no, or only slight impairment. Furthermore, there is no clear dose-effect relationship established yet for toluene and colour vision effects. It is also unclear whether the impairment of colour vision that occurs following inhalation exposure to toluene is due solely to neurological effects damage or if it also involves direct effects on ocular tissue (ATSDR, 2000). Toluene exposure has been shown to cause eye irritation in a number of human and animal studies; however, no studies were identified that examined eyes for structural damage (ATSDR, 2000).

In a recent multicenter study of 12 rotogravure facilities in Germany, Gericke *et al.* (2001) evaluated the potential adverse health effects associated with long term toluene exposure. Information on exposure and medical data was compiled for 1,077 male workers. Evaluations included: physical examination, standard tests of psycho-physiological and psycho-motor performances, self-reporting of subjective symptoms, and data from a variety of laboratory blood tests. A small reference group (n=109) was selected from companies within the paper industry. Considering only the end points evaluated, as well as the apparent limitations of the study, the authors concluded that there is no evidence that long term occupational toluene exposure in the rotogravure industry is associated with chronic adverse health effects.

A large number of subchronic and chronic inhalation toxicology studies have been conducted for toluene in experimental animals. Selected relevant studies are described in the following paragraphs.

Forkman *et al.* (1991) exposed male Sprague-Dawley rats to 0 or 3,700 mg/m^3 for 21 hours a day, 5 days per week for 4 weeks. The rats were either pre-trained in performance test behaviour prior to exposure or exposed and then trained. Following exposure, rats were subjected to several behavioral tests, which were performed from 11 to 35 days post-exposure. Exposure of pre-trained rats to toluene resulted in significantly different overall test performances when compared to controls. Rats trained after toluene exposure also had overall test performances that differed from controls, but these differences were not statistically significant.

Korsak *et al.* (1992) reported that rats exposed to toluene concentrations at 1,000 ppm or 100 ppm (3,750 or 375 mg/m^3) for 6 hours a day, 5 days per week, for 3 or 6 months, respectively, showed a statistically significant decrease in motor function. This decreased motor function was based on reduced performance (by approximately 60% and 65% of control performance) at 1,000 and 100 ppm toluene, respectively, in the rotarod test and decreases in spontaneous motor activity (62% of control) at 100 ppm.

von Euler *et al.* (1993) exposed rats to 80 ppm (300 mg/m^3) toluene, for 6 hours a day, 5 days per week, for 4 weeks. Spatial learning (at post-exposure days 3 to 6) and memory (at post-exposure day 14) were tested using a water maze. Spontaneous and apomorphine-induced locomotor activity was evaluated on post-exposure day 17. Dopamine binding was also evaluated in this study. It was found that toluene exposure at 80 ppm caused a statistically significant impairment in spatial learning and memory. Toluene exposure also significantly increased apomorphine-induced locomotion and motility, but not rearing. Spontaneous locomotion, motility and rearing were not affected. Toluene exposure also significantly increased dopamine-mediated locomotor activity and the number of dopamine D2 receptors in the neostriatum of rat brains.

Poon *et al.* (1994) exposed male and female rats to 30 or 300 ppm (113 or 1,125 mg/m^3) toluene for 6 hours a day, 5 days per week for 4 weeks. Rats of both sexes showed histopathological changes in the tracheal epithelium at both exposure levels. Alkaline phosphatase activity was significantly elevated in male rats exposed to 300 ppm. Female rats exposed to 30 or 300 ppm showed a treatment-related reduction in follicle size of the thyroid.

In an early study, von Oettingen *et al.* (1942) reported that rats exposed to 600 ppm (2,250 mg/m^3) for 7 hours a day, for 5 weeks, showed irritation of the lung. Rats exposed to 2,500 and 5,000 ppm (9,375 and 18,750 mg/m^3) for the same duration had pulmonary lesions. Inhalation of 600 to 5,000 ppm over this duration resulted in the formation of renal casts within the collecting tubules of rat kidneys. A concentration of 2,500 ppm toluene also produced a lack of coordination in the rats.

In a study by CIIT (1980), also reported as Gibson and Hardisty (1983), Fischer 344 rats of each sex were exposed to 0, 30, 100 or 300 ppm (0, 113, 377 or 1,130 mg/m^3) of 99.9% pure toluene for 6 hours a day, 5 days per week, for 106 weeks. The duration-adjusted concentrations were reported be 0, 20, 67 or 202 mg/m^3 (U.S. EPA, 1992). There were no significant treatment-related effects reported in the exposed animals. While male rats exposed to 300 ppm had a significant increase in body weight relative to controls, no concentration-response trend was evident. By the end of the study, female rats exposed to 100 or 300 ppm exhibited a slight but statistically significant reduction in hematocrit, and an increase in the mean corpuscular hemoglobin concentration was noted in the 300 ppm females only. The highest concentration examined in this study, 300 ppm, was designated as a NOAEL by the study team.

A study by API (1981) exposed Sprague-Dawley rats to cumulative mean exposures of 0, 100 or 1,481 ppm (0, 377 or 5,653 mg/m^3) toluene, for 6 hours a day, 5 days per week, for 26 weeks. The duration-adjusted human-equivalent concentrations were reported to be 0, 67 and 1,009 mg/m^3 by U.S. EPA (1992). No significant treatment-related effects were reported in this study. Thus, a study NOAEL of 1,481 ppm (5,653 mg/m^3) was identified.

A reproductive toxicity study by Ono *et al.* (1996) reported the following effects in the parental generation. Male rats exposed to 2,000 ppm (7,500 mg/m^3) toluene for 90 days showed an increase in kidney weights, necrosis of kidney tubules, and decreased thymus weights. Pregnant female rats exposed to 2,000 ppm for 6 hours a day, for 21 days showed lacrimation. A previous study (Ono *et al.*, 1995) found that pregnant dams exposed to 600 ppm (2,250 mg/m^3) for 6 hours a day during gestation days 7 to 17 also had reduced thymus weights.

Pryor (1991) reported that body weight decreased in rats exposed to 2,000 ppm (7,500 mg/m^3) of toluene, for 8 hours a day, 7 days per week for 11 weeks. In addition, exposure of rats to concentrations of 2,273 ppm (8,524 mg/m^3) for 8 hours a day for 16 weeks, or to the range of 2,200 to 6,200 ppm (8,250 to 23,250 mg/m^3) toluene intermittently, for 8 hours a day, 15 to 60 minutes/hour, over 23 weeks, caused a shortening and widening in the gait.

Mattsson *et al.* (1990) exposed rats to 8,000 ppm (30,000 mg/m^3) toluene for 15 to 35 minutes, 4 to 9 times per day, 5 days per week for 13 weeks. It was reported that flash-evoked potential (FEP) responses were abnormal in the exposed rats. The FEP response test measures the electrical response of the visual components of the nervous system to a high intensity flashing strobe light. It is considered that a distortion of the FEP waveform indicates an impaired visual response to light (ATSDR, 2000).

Korbo *et al.* (1996) exposed rats to 1,500 ppm (5,625 mg/m^3) toluene for 6 hours a day, 5 days per week for 6 months, followed by a four-month recovery period. After this recovery period, it was found that the number of neurons in the rat hippocampus were reduced relative to controls. The hippocampus is an important area in the brain for memory and learning processes (ATSDR, 2000).

In a 2-year bioassay (NTP, 1990), Fischer 344 rats of each sex were exposed to 0, 600 or 1,200 ppm (0, 2,261 or 4,523 mg/m^3) toluene for 6.5 hours a day, 5 days per week, for 103 weeks. U.S. EPA (1992) reported duration-adjusted concentrations as 0, 437 and 875 mg/m^3, respectively. Mean body weights in both exposed groups did not differ from controls for either sex. There were no exposure-related clinical signs of toxicity reported, and survival rate was similar between all groups. At an interim sacrifice point in the study, there was a mild to moderate degeneration observed in the olfactory and respiratory epithelium of the nasal cavity in 39 of 40 rats in the 600 and 1,200 ppm groups. This only occurred in 7 of 20 controls. At the end of the two-year study, there was a significant increase observed in the incidence of erosion of the olfactory epithelium (males: 0 of 50, 3 of 50 and 8 of 49; females: 2 of 49, 11 of 50 and 10 of 50; at 0, 600 and 1,200 ppm, respectively). There was also significant degeneration of the respiratory epithelium (males: 15 of 50, 37 of 50 and 31 of 49; females: 29 of 49, 45 of 50 and

39 of 50; at 0, 600 and 1,200 ppm, respectively). Females in the 600 and 1,200 ppm groups also showed a significant increase in inflammation of the nasal mucosa (27 of 49, 42 of 50 and 41 of 50 at 0, 600 and 1,200 ppm, respectively) and respiratory metaplasia of the olfactory epithelium (0 of 49, 2 of 50 and 6 of 50 at 0, 600 and 1,200 ppm, respectively). A LOAEL of 600 ppm (2,261 mg/m^3) toluene was identified from this study for the concentration-dependent increase in erosion of the olfactory epithelium in male rats, and degeneration of the respiratory epithelium in both sexes. No NOAEL could be identified.

NTP (1990) also conducted a 14 to 15 month study where Fischer 344/N rats of both sexes were exposed to toluene at 0, 100, 625, 1,250, 2,500 and 3,000 ppm (0, 377, 2,355, 4,711, 9,422 and 11,307 mg/m^3, respectively), for 6.5 hours a day, 5 days per week. The U.S. EPA (1992) reported duration-adjusted concentrations as 0, 73, 455, 911, 1,823 and 2,187 mg/m^3, respectively. Eight of 10 males exposed to 3,000 ppm died during the second exposure week. No females died at any concentration tested. Final body weights were 15 and 25% lower in males, and 15% and 14% lower in the females of the 2,500 and 3,000 ppm groups, respectively, relative to controls. A concentration-related increase was noted in relative liver weights, which was significant in the 1,250, 2,500 and 3,000 ppm groups for males and in the 2,500 and 3,000 ppm groups for females. Relative weights of the heart, lung, kidney and right testis were also significantly elevated in the 2,500 and 3,000 ppm groups when compared to controls, although no histopathological lesions were observed in any exposure group. A LOAEL of 2,500 ppm [which equates to a LOAEL (human equivalency concentration or HEC) of 1,823 mg/m^3] was identified based on decreased body weight gain in both males and females; a NOAEL for this effect was identified to be 1,250 ppm [NOAEL(HEC) of 911 mg/m^3].

The two-year NTP (1990) study also evaluated mice. B6C3F1 mice of both sexes were exposed to 0, 120, 600 or 1,200 ppm (0, 452, 2,261 or 4,523 mg/m^3, respectively) toluene for 6.5 hours a day, 5 days per week for 2 years. Duration-adjusted concentrations were reported to be 0, 87, 47 and 875 mg/m^3, respectively, but the U.S. EPA (1992). Mean body weights did not differ significantly among groups and no treatment-related clinical signs of toxicity were reported. While deaths occurred in all exposure groups, they were considered unrelated to toluene exposure and were similar to mortality rate in the controls. An excess incidence of non-neoplastic inflammatory lesions of the urinary and genital system was observed in all male exposed male mice groups. At the 15-month interim sacrifice point, minimal hyperplasia was observed in the bronchial epithelium in 4 of 10 females in the 1,200 ppm group. By study termination, there was a concentration-dependent increase in the incidence of splenic pigmentation in exposed males (9 of 60, 11 of 60 and 18 of 59 at 120, 600 and 1,200 ppm, respectively) relative to controls (4 of 60). In females, this incidence was 37 of 50, 33 of 50, 34 of 49 and 28 of 47 at 0, 120, 600 and 1,200 ppm, respectively. The occurrence of endometrial hyperplasia was noted in 14% of females in the 1,200 ppm group. This effect only occurred in 4% of the females in the other exposure groups and controls. No differences were noted between the exposed and control groups for either sex in the incidence of degeneration of either the olfactory or respiratory epithelium. As no adverse effects were noted in this study, the highest concentration, 1,200 ppm was identified as a NOAEL in mice. This equates to a NOAEL(HEC) of 875 mg/m^3.

A number of studies have investigated the ototoxicity of toluene in subchronic studies with experimental animals. Exposure of rats to 1,200 ppm (4,500 mg/m^3) for 14 hours a day, for 5 to

9 weeks or 1,000 ppm (3,750 mg/m^3) for two weeks caused a permanent loss of hearing in the high frequency range (approximately 16 kHz) (Pryor and Rebert, 1992; Pryor *et al.*, 1984a,b). Hearing loss in rats appears to occur independently of whether or not exposure is continuous or episodic (Pryor, 1991). Hearing loss in rats is also compounded by post-toluene-exposure high noise levels (Johnson *et al.*, 1988). Combined exposure to toluene and noise produces a greater loss of hearing function in rats than exposure to either toluene alone or noise alone (Lataye and Campo, 1997). Campo *et al.* (1997) found that hearing loss occurred in rats after exposure to 1,750 ppm (6,563 mg/m^3) toluene for 6 hours a day, 5 days per week for 4 weeks (Campo *et al.*, 1997). Pryor *et al.* (1984a) reported that high frequency hearing loss is more severe in weanling rats than in young adult rats, following exposure to 1,200 ppm toluene for 14 hours a day, for 5 weeks. The studies by Pryor *et al.* (1984a,b) also reported that hearing loss was observed after as few as 2 weeks exposure to 1,000 ppm toluene for 14 hours a day, while concentrations of 700 ppm (2,625 mg/m^3) for 14 hours a day produced no effect on hearing even after 16 weeks of exposure. Intermittent exposure to 3,000 ppm (11,250 mg/m^3) for 30 minutes per hour, for eight hours a day caused hearing loss within two weeks, whereas a similar exposure schedule for only four hours a day caused no adverse auditory effects after nine weeks. From these studies, the U.S. EPA (1992) identified a NOAEL for hearing loss in rats of 700 ppm. This was converted by U.S. EPA to a duration adjusted NOAEL(HEC) of 1,100 mg/m^3.

Hearing loss in rats is exacerbated by co-exposure to other organic chemicals such as ethanol or acetyl salicylic acid (Campo *et al.*, 1998; Johnson, 1992). In addition, when rats are pre-exposed to a substance which stimulates MFO induction in the liver prior to toluene exposure, hearing loss occurs to a much lesser degree; whereas rats that are not pre-exposed do experience hearing loss (Pryor *et al.*, 1991). This suggests that toluene itself, rather than a metabolite, is responsible for the effects on hearing.

Lataye *et al.* (1999) exposed Long-Evans rats to 1,750 ppm (6,563 mg/m^3) of toluene for 6 hours a day, 5 days per week, for 4 weeks. Electrocochleographic findings showed a hearing deficit not only in the mid-frequency region (12 to 16 kHz), but also in the mid-low-frequency region (3 to 4 kHz). The effect of toluene was also independent of the frequency in this experiment. Histological analysis showed a broad loss of outer hair cells in both mid- and mid-apical coil of the organ of Corti.

Davis *et al.* (2002) exposed 33 chinchillas to a 95 dBA 500 Hz octave band noise plus 2,000 ppm (7,500 mg/m^3) toluene, for 8 or 12 hours a day for 10 days. Auditory function was estimated using the auditory brainstem response (ABR) to tones between 500 Hz and 16 kHz. Toluene alone had no effect on the ABR, while noise alone produced a threshold shift. There was also no interaction of noise and toluene. The results suggest that chinchillas are less susceptible to the ototoxic effect of toluene than mice and rats. The authors suggest that this lower sensitivity is due to the chinchilla liver having a greater capacity to detoxify toluene. This study also noted that chinchilla livers contain more of the P450 enzymes CYP2E1 and CYP2B than either rats or humans, and that the P450 enzymes are more active in chinchillas than in rats and humans. Clearly, there are species differences with respect to toluene ototoxicity that must be considered in attempting to extrapolate the results of such studies to human exposure situations. Rats and mice appear to be an appropriate model for human toluene ototoxicity (Davis *et al.*, 2002).

Although the results of subchronic ototoxicity studies clearly indicate that hearing loss occurs following inhalation exposure to elevated toluene concentrations in rats, the significance of these findings to humans is not well understood. For example, among chronic toluene abusers there is only a single report of adverse effects on hearing (*i.e.*, Metrick and Brenner, 1982).

Tables 8 and 9 summarize the relevant subchronic and chronic inhalation NOAELs, LOAELs, and other endpoints that were reported in the human and animal studies described above.

Table 8 Summary of Subchronic and Chronic Toluene Inhalation Toxicology Studies in Humans

Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
5.7 years (average)	332 (average)	LOAEL: 332 mg/m^3 for neurobehavioural effects	Foo *et al.*, 1990
16 years (average)	97 to 232	Haematological effects	Stengel *et al.*, 1998
1 to 36 years	311	Effects to cardiac autonomic function	Murata *et al.*, 1993
12 to 14 years	364	Auditory alterations	Abbate *et al.*, 1993
21.6 years (approximate)	150 to 225	Effects to sensory-evoked potentials	Schaper *et al.*, 2003
Not reported	585	Impaired colour vision (colour confusion index significantly greater)	Zavalic *et al.*, 1998a
Not reported	450	Impaired colour vision	Zavalic *et al.*, 1998b

Table 9 Summary of Subchronic and Chronic Toluene Inhalation Toxicology Studies in Experimental Animals

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
Rats	6 h/d, 5 d/wk for 3 or 6 months	377, 3,770	Statistically significant decrease in motor function;	Korsak *et al.*, 1992
Rats	6 h/d, 5 d/wk for 4 wks	302	Statistically significant impairment in spatial learning and memory	von Euler *et al.*, 1993
Rats	6 hours a day, 5 d/wk for 4 wks	113, 1,130	Histopathological changes in tracheal epithelium	Poon *et al.*, 1994
Rats	6 h/d, 5 d/wk for 106 wks	0, 113, 377, 1,130	NOAEL: 1,130 mg/m^3	CIIT, 1980; Gibson and Hardisty, 1983
Rats	6 h/d, 5 d/wk for 26 wks	0, 377, 5,653	NOAEL: 5,653 mg/m^3	API, 1981
Rats (male)	90 days	7,540	Increased kidney weights, necrosis of kidney tubules, decreased thymus weights	Ono *et al.*, 1996
Rats (pregnant)	6 h/d for 21 d	7,540	Lacrimation	Ono *et al.*, 1996
Rats (pregnant)	6 h/d during gestation d 7 – 17	2,262	Reduced thymus weights	Ono *et al.*, 1995
Rats	6.5 h/d, 5 d/wk for 103 wks	0, 2,261, 4,523	LOAEL: 2,261 mg/m^3 for increased erosion of the olfactory epithelium; degeneration of respiratory epithelium	NTP, 1990
Rats	6.5 h/d, 5 d/wk	0, 377, 2,355,	LOAEL: 9,422 mg/m^3 for decreased	NTP, 1990

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
	for 14 – 15 months	4,711, 9,422, 11,307	body weight gain; LOAEL (HEC) 1,823 mg/m^3 NOAEL: 4,711 mg/m^3; NOAEL(HEC): 911 mg/m^3	
Mice	6.5 h/d, 5 d/wk for 2 years	0, 452, 2,261, 4,523	NOAEL: 4,523 mg/m^3; NOAEL(HEC): 875 mg/m^3	NTP, 1990
Rats	various	various	NOAEL: 2,639 mg/m3 (for lack of hearing loss) NOAEL(HEC): 1,100 mg/m^3	Derived by U.S. EPA, 1992 based on several studies
Rats	6 h/d, 5 d/wk for 4 wks	6,597	Hearing loss	Lataye *et al.*, 1999

4.1.4 Developmental and Reproductive Toxicity

There are few human studies available that investigated the reproductive or developmental effects of toluene following inhalation exposure. Overall, the human data that exists does not provide convincing evidence that toluene causes reproductive effects in humans (ATSDR, 2000).

A number of developmental toxicity studies with rats, mice and rabbits exposed *via* inhalation to toluene indicate that toluene is not a potent teratogen at exposure levels below those that induce maternal toxicity, but it can retard fetal growth and skeletal development and cause behavioural alterations in offspring (ATSDR, 2000). It should also be recognized that the available developmental toxicity studies are limited by issues such as unknown or unconventional exposure durations, poorly quantified exposures, co-exposure to other solvents, inadequate descriptions of maternal toxicity, use of individual offspring instead of litters for statistical analyses, and unknown purity of toluene used (Donald *et al.*, 1991).

Ng *et al.* (1992a) reported that exposed female workers at an audio speaker factory did not report increased incidence of menstrual cycle irregularities, altered extent of uterine bleeding, or occurrence of dysmenorrhea. However, Ng *et al.* (1992b) reported a significant increase in spontaneous abortion for these workers. Specifically, workers exposed to 50 to 150 ppm toluene (mean=88 ppm; 330 mg/m^3) for 10 years had a 12.4% incidence, compared with a 2.9% incidence in workers exposed to 0 to 25 ppm (0 to 94 mg/m^3) toluene and 4.5% incidence in unexposed controls from the general population. The majority of women examined did not smoke or drink and were of similar socioeconomic status. The authors consider that potential confounding by exposure to chemicals other than toluene was minimized by inclusion of controls who carried out similar types of work, but did not use toluene-based adhesives.

The incidence of spontaneous abortions was reported to be elevated over general population incidence rates in five exposed female workers (Lindbohm *et al.*, 1992) and among the wives (n=28 or 48) of exposed male workers (Lindbohm *et al.*, 1992; Taskinen *et al.*, 1989). These studies are of limited value as exposure levels were not reported and only a small number of cases were evaluated.

Svensson *et al.* (1992a, b) reported that exposure to increasing concentrations of toluene (8 to >111 ppm; 30 to >416 mg/m^3)) was associated with decreased plasma levels of luteinizing hormone, follicular stimulating hormone and testosterone levels in two groups of 20 or 47 males occupationally exposed for a period of 0.5 to 39 years. Average toluene air concentrations were reported to be 36 or 29 ppm (135 or 109 mg/m^3) for the two groups, respectively. It is not known how changes in these hormone levels would affect reproductive success. The observed effects may be due to toluene effects on the catecholamine hormones of the hypothalamus or a consequence of toluene or a metabolite behaving as a dopamine agonist (ATSDR, 2000).

Hersh *et al.* (1985) described clinical and morphometric characteristics common to three children whose mothers had abused toluene for a period of four to five years, including during their pregnancies. Clinical findings common to these three children included microcephaly, CNS dysfunction, attention deficits, developmental delays and mental deficiency. The children had a small midface, deep-set eyes, small jaws and blunting of the fingertips. Wilkins-Haug and Gabow (1991) reported that preterm delivery, perinatal death and growth retardation were significantly increased among 21 newborns exposed whose mothers abused toluene.

McDonald *et al.* (1987) conducted a retrospective case/control study that examined the history of chemical exposure in 301 women who had recently given birth to an infant with a major congenital defect. Among the findings were that only exposure to aromatic solvents showed a clear excess of defects, which mostly occurred in the urinary tract. Of 19 of these urinary tract defect cases reviewed, toluene was identified as the major solvent in 11 cases. However, toluene was not the only solvent these women were exposed to, thus it is difficult to make conclusions about the developmental effects of toluene in this study.

Luderer *et al.* (1999) exposed women in the follicular and luteal phases of the menstrual cycle and men, to 0 or 50 ppm (0 or 188 mg/m^3) toluene through a mouthpiece for three hours. Blood was sampled at 20-minute intervals for three hours before, three hours during, and three hours after exposure. Plasma LH, FSH, and testosterone were measured. In men, the mean concentrations of LH showed a significant interaction between exposure and sampling period, with a greater LH decline during exposure to toluene than during sham exposure. However, there was no concomitant effect on testosterone concentrations. The LH pulse frequency of women in the luteal phase showed a significant interaction between exposure and sampling period, with a greater decline in pulse frequency during exposure to toluene than during sham exposure. No other significant effects of toluene exposure were noted. It was concluded that three-hour exposure to 50 ppm toluene did not result in abnormal episodic LH or FSH secretion profile; however, subtle effects on LH secretion in men and women in the luteal phase occurred. However, the clinical relevance of these effects is unclear.

Ono *et al.* (1996) reported significantly decreased sperm counts (26%) and decreased weights of the epididymis (15%) in male rats exposed to 2,000 ppm (7,500 mg/m^3) for 6 hours a day, for 90 days, including 60 days prior to mating with females that were exposed to the same concentration for 14 days before, and 7 days after mating. At a lower concentration tested (600 ppm; 2,250 mg/m^3)), a slight decrease in sperm count (13%) was observed, but histological examination showed no testes or epididymis abnormalities. There were also no such abnormalities at 2,000 ppm. No significant exposure-related effects on mating behavior or fertility indices were observed in this study.

Female rats exposed to 3,000 ppm (11,250 mg/m^3) toluene for seven days showed a number of changes in the ovarian tissue, including abundant vacuoles, lytic areas, and mitochondrial degeneration in the antral follicles (Tap *et al.*, 1996).

Thiel and Chahoud (1997) found no effects on mating, fertility, or pregnancy indices for F1 rats that were exposed *in utero* to 1,200 ppm (4,500 mg/m^3) toluene for six hours a day during gestational days 9 to 21. The offspring of rats exposed to 1,200 ppm toluene showed a significant reduction in fetal weight, a delay in physical development (vaginal opening) and higher mortality until weaning relative to controls. Rats exposed to 1,000 ppm (3,750 mg/m^3) under the same conditions and duration showed significantly reduced body weights at birth, and developmental delays. No such effects were observed in rats exposed to 300 or 600 ppm (1,125 or 2,250 mg/m^3) for six hours a day during gestational days 9 to 21. In rat offspring from the 300, 600, 1,000 and 1,200 ppm groups, it was found that there were no consistent concentration-dependent performance deficits (relative to controls) in tests of reflexes, balance on a rotating rod, locomotor activity, or discrimination learning, evaluated at several ages.

Ono *et al.* (1999) exposed male Sprague-Dawley rats to toluene at air concentrations of 0, 4,000 or 6,000 ppm (0, 15,000 or 22,500 mg/m^3), for two hours a day, for five weeks. Non-reproductive effects included an exposure-related suppression of body weight gain and food consumption. Salivation and lacrimation were also observed during exposure periods and intensified with repeated exposure. Rats in the 6,000 ppm group also had decreased spleen and thymus weights, as well as suppressed lymphocyte counts. Reproductive effects were only observed in the 6,000 ppm group. In this group, epididymal sperm counts, sperm motility, sperm quality and *in vitro* penetrating ability to zona-free hamster eggs were all significantly reduced. There were no exposure-related changes in testes weight or spermatogenesis within testes. Tail-less sperm heads were observed within zona-free eggs incubated with sperm from rats of the 6,000 ppm group, but not control rats. There were no significant changes reported in serum luteinizing hormone, follicle-stimulating hormone, or testosterone levels at one month post-exposure in rats of the 6,000 ppm group. The authors suggest that high concentrations of toluene may target sperm in the epididymis and disrupt sperm maturation.

Hudak and Ungvary (1978) exposed three groups of pregnant CFY rats to toluene during different periods of gestation and for differing exposure durations. Two groups had their own control group exposed to air only. The first group was exposed to 1,500 mg/m^3 for 24 hours a day during gestational days 9 to 14. Two dams died during this experiment. No details on deaths were provided but no other maternal toxicity was reported. Fetotoxicity was manifested as sternebral alterations (6% versus 1% in controls), extra ribs (22% versus 0% in controls), and the presence of fetuses with missing tails (2 of 213 versus none in controls). In this experiment, 1,500 mg/m^3 is a LOAEL for fetotoxicity and a frank effect level (FEL) for maternal toxicity. The second group received this same concentration continuously, but only on gestational days 1 to 8. Five dams died in this experiment, although toxicity parameters of the surviving dams were identical with the controls from the first group. Slight hydrocephaly was noted in four fetuses (all from one litter), and 17% growth retardation was observed (versus 7% in the controls. The third group of rats was exposed to 1,000 mg/m^3 for eight hours a day from gestational days 1 to 21. No maternal deaths or toxicity occurred. Minor skeletal retardation occurred in the exposed fetuses (25%) versus 0% in controls (0%). The results of this experiment indicate that 1,000 mg/m^3 is a LOAEL for developmental effects. This concentration is also a NOAEL for maternal effects.

Hudak and Ungvary (1978) also exposed groups of pregnant CFLP mice to 0 or 500 or 1,500 mg/m^3 toluene continuously, during gestational days 6 to 13. All mice in the high exposure group died within 24 hours. No dams died in the low exposure group (500 mg/m^3). In this group, the average fetal weight decreased by roughly 10%, and the percentage of weight-retarded fetuses increased to 27.6% from 6.5% in controls. There was no difference observed in incidence of skeletal malformations or anomalies between this group and controls. From this experiment, 1,500 mg/m^3 is a FEL and 500 mg/m^3 is a mild LOAEL. The U.S. EPA (1992) considers 500 mg/m^3 a LOAEL(HEC) as duration adjustment is not typically performed for developmental effects.

A preliminary gestational exposure study reported extreme maternal toxicity and marked resorption of fetuses in pregnant rats exposed to 5,000 ppm (18,750 mg/m^3) toluene for six hours a day on gestational days 6 to 15 (Huntingdon Research Centre, 1992a). At 3,500 ppm (13,125 mg/m^3), there was significantly decreased mean fetal body weight (roughly 20% relative to controls). In a followup study, rats were exposed to 250, 750, 1,500 or 3,000 ppm (938, 2,813, 5,625 or 11,250 mg/m^3), toluene for six hours a day on gestational days 6 to 15 (Huntingdon Research Centre, 1992b). No effects were noted for either maternal or fetal survival, but mean fetal body weights were significantly decreased (8 to 14%) in the 1,500 and 3,000 ppm groups. The percentage of fetuses with unossified sternebrae was significantly increased in the 3,000 ppm group (60% versus 37% in controls). Overall, the incidences of fetuses or litters with skeletal or visceral malformations were increased in a statistically significant manner in the 250, 1,500 and 3,000 ppm groups, but no exposure-response trend was evident.

Ono *et al.* (1995) exposed pregnant Sprague-Dawley rats to 600 or 2,000 ppm (2,250 or 7,500 mg/m^3) toluene for six hours a day from gestational day 7 to 17. A control group inhaled "conditioned" clean air. At 2,000 ppm, there was maternal toxicity that consisted of body weight suppression, and there was also reduced body weights in offspring, high fetal mortality, and embryonic growth retardation at 2,000 ppm. No external, internal, or skeletal anomalies were observed in the fetuses of either exposed group. In addition, offspring from the exposed groups showed no significant differences from controls based on the results of pre- and post-weaning behavioral and physiological tests (*i.e.*, tests of reflexes, locomotor activity, balance on a rotating rod, learning ability, eye opening). As no toluene-related changes could be identified in the 600 ppm group, this concentration was considered a NOAEL.

Ungvary and Tatrai (1985) exposed New Zealand rabbits to 0, 500 or 1,000 mg/m^3 toluene, for 24 hours a day, on gestational days 7 to 20. CFLP mice were exposed to 0, 500, 1,000 or 1,500 mg/m^3 toluene, also for 24 hours a day, on gestational days 6 to 15. All female mice exposed to 1,500 mg/m^3 died. In the mice exposed to 1,000 mg/m^3, there was an increase in fetuses with retarded weight and in fetuses with skeletal retardation, relative to controls. Mice in the 500 mg/m^3 group did not differ from controls with respect to these effects. Of eight pregnant rabbits exposed to 1,000 mg/m^3, two died, four had spontaneous abortions, and the remaining two had total litter resorption. No deaths occurred in rabbits exposed to 500 mg/m^3 but 1 of 10 rabbits had a spontaneous abortion. From this study, the U.S. EPA (1992) determined a NOAEL(HEC) of 500 mg/m^3 for reproductive effects in mice. For rabbits, 500 mg/m^3 concentration is considered a LOAEL.

Courtney *et al.* (1986) exposed pregnant CD-1 mice to 0, 200 ppm or 400 ppm (0, 754 and 1,508 mg/m^3) toluene, for seven hours a day during gestational days 7 to 16. Maternal effects reported included reduced relative liver weight in both exposed groups, relative to controls, and a statistically significant increase in lactate dehydrogenase activity in the brain of dams in the 400 ppm group. In the two exposed groups, there were no significant differences in the number of implantation sites, number of live fetuses, fetal deaths, or fetal body weights, relative to controls. A statistically significant increase over controls in the incidence (both per litter and per fetus) of enlarged renal pelves was noted in dams exposed to 200 ppm but not 400 ppm. A statistically significant difference from controls in fetal rib profile (percent fetuses with one or two additional or fewer ribs) was also reported for fetuses from dams exposed to 400 ppm, but not 200 ppm. As no clearly significant toxicological effects were observed in this study, the U.S. EPA (1992) identified 400 ppm as the reproductive and developmental NOAEL [NOAEL(HEC) = 1,508 mg/m^3].

In rabbits exposed to 30, 100, 300 or 500 ppm toluene (113, 375, 1,125 or 1,875 mg/m^3), for six hours a day on gestational days 6 to 18, there were no signs of maternal toxicity, and no significant effects were observed related to fetal weight or survival, pre- or postimplantation losses, or incidences of fetuses with external, soft-tissue, or skeletal variations or malformations, relative to controls (Klimisch *et al.*, 1992).

Groups of rat pups exposed to toluene (at 100 or 500 ppm; 375 or 1,875 mg/m^3), for 12 hours a day, from postnatal days 1 to 28, had smaller volumes of the granular cell layer of the area dentate of the hippocampus, relative to controls (Slomianka *et al.*, 1990). However, once rats in the 500 ppm group had recovered for 92 days, these changes were found to be reversible (Slomianka *et al.*, 1992).

Da Silva *et al.* (1990) exposed rats and hamsters to 0 or 800 mg/m^3 toluene for six hours a day on gestational days 14 to 20 (rats), or gestational days 6 to 11 (hamsters). The exposed rats demonstrated a significant exposure-related decrease in birth weight relative to controls. In addition, the number of live rat pups was significantly reduced in the 800 ppm group. In rat offspring, the only effect noted was a shortened first trial latency in choosing one side of a maze. However, this effect was minimal and its significance is unclear. There were no observed reproductive abnormalities in exposed hamsters. The only effect noted in neurobehavioral tests of hamster offspring was an equivocal reduction in rotarod performance. No developmental neurobehavioral effect levels could be identified in this study, although it appears that the rat developmental processes are more sensitive than those of the hamster.

A 2-generation inhalation reproductive study was conducted in CD rats by API (1985). Rats were exposed to toluene at 0, 100, 500 or 2,000 ppm (0, 377, 1,885 or 7,538 mg/m^3, respectively) for 6 hours a day, 7 days per week for 80 days and during a 15 day mating period.

Mated females were then exposed to the same concentrations during gestational days 1 to 20, and during lactational days 5 to 20. After weaning, F1 pups were exposed 80 times and then randomly mated with members of the same exposure group (2 females/1 male) to produce the second generation (F2). It was reported that mean male body weights were slightly reduced in the first two weeks of exposure in the 500 and 2,000 ppm groups, although this effect appeared un-related to exposure. There were no differences observed in male or female fertility indices, length of gestation, mean numbers of viable and nonviable pups at birth, or pup survival indices during lactation. No abnormal histopathology was noted in any organs examined. There was a significant decrease in weight of the F1 offspring, relative to controls. This decrease persisted throughout the lactation period in the pups from dams exposed to 2,000 ppm, and in those of an ancillary group in which females exposed to 2,000 ppm were mated with males that were not exposed. No data were provided regarding the F2 generation. Based on the effects on F1 pups, a LOAEL of 2,000 ppm [LOAEL(HEC) = 7,538 mg/m^3], and a NOAEL of 500 ppm [NOAEL(HEC) = 1,885 mg/m^3], were identified by U.S. EPA (1992).

A very similar study to API (1985) was reported in Roberts *et al.* (2003). This study team conducted a 2-generation reproductive toxicology study in which male and female Sprague-Dawley rats, parental (F0) and first generation (F1), were exposed to toluene *via* whole body inhalation, for 6 hours a day, 7 days per week for 80 days during premating and for 15 days during mating at concentrations of 0, 100, 500 and 2,000 ppm (0, 375, 1,875 and 7,500 mg/m^3). Pregnant females at all dose levels were exposed from gestation day 1 to 20 and lactation day 5 to 21. F1 pups that were selected to produce the F2 generation were treated for 80 days beginning immediately after weaning (lactation day 21) and initially mated at a minimum of 100 days of age. F2 pups were not exposed to toluene. It was found that toluene exposure did not induce adverse effects on fertility, reproductive performance, or maternal/pup behaviours during the lactation period in males and females of the F0 or F1 generation, but did inhibit growth in F1 and F2 offspring at 2,000 ppm (when both sexes treated) and 2,000 ppm (when females only were treated). Reduced fetal body weight and skeletal variations were observed upon Caesarean section of selected 2,000 ppm (both sexes treated) dams at gestation day 20. Exposure at 2,000 ppm to F0 males did not induce a similar weight inhibition in offspring. The authors identified a reproductive NOAEL of 500 ppm in the groups in which female rats were exposed and 2,000 ppm for groups in which only males were treated.

Shigeta *et al.* (1982) reported statistically significant increases in the number of fetal resorptions in the offspring of mice exposed to 100 ppm (375 mg/m^3) toluene for six hours a day on gestational days 1 to 17. A concentration of 1,000 ppm (3,750 mg/m^3) resulted in a statistically significant increase in the incidence of extra ribs.

Hass *et al.* (1999) exposed rats to 0 or 1,200 ppm (0 or 4,500 mg/m^3) toluene for six hours a day from gestational day 7 until postnatal day 18. Developmental and neurobehavioral effects in the offspring were investigated using a test battery that included tests of physical development, reflex development, motor function, motor activity, sensory function and learning and memory. There was no observed maternal toxicity or decreased offspring viability. However, lower birth weight, delayed development of reflexes and increased motor activity in the open field was observed in the offspring of exposed rats. In addition, exposed female offspring also had poorer scores on a Morris water maze test, relative to controls.

Dalgaard *et al.* (2001) conducted two developmental toxicity experiments in rats. In one study, pregnant Wistar rats were exposed to 1,200 ppm (4,500 mg/m^3) toluene for six hours a day, from gestational day 7 to postnatal day (PND) 18. Sperm analysis was performed in the adult male offspring at PND 110. Toluene exposure did not affect the semen quality in rats. In the second study, pregnant rats were exposed to 1,800 ppm (6,750 mg/m^3) from gestation days 7 to 20, and the male offspring were killed at PND 11, 21 or 90. Mean body weight in pups of exposed dams was lower than controls. By PND 21 and 90, the body weight of exposed males was similar to that of the controls. Absolute and relative testes weights were reduced, although the reduction was not statistically significant. Histopathological examinations of the testis revealed no differences between exposed and control animals. A marked increase in number of apoptotic cells was observed in cerebellar granule cells at PND 21 compared with PND 11 and PND 90 groups. It was concluded that neither pre- and postnatal exposure to 1,200 ppm, nor prenatal exposure to 1,800 ppm induced significant reproductive effects. However, prenatal exposure to 1,800 ppm toluene increased neuronal apoptosis in the cerebellum of weaned male rats, possibly by delaying postnatal migration of granule cells to the cerebellum, or by general retardation of fetal growth (Dalgaard *et al.*, 2001).

Hougaard *et al.* (2003) found that pregnant rats exposed to 1,500 ppm (5,625 mg/m^3) toluene for six hours a day during the last two weeks of gestation showed reduced birth weight of pups and lower maternal weight gain. A depressant effect of toluene on maternal corticosterone levels was also observed.

Table 10 summarizes the relevant reproductive and developmental inhalation toxicology studies conducted with experimental animals.

Table 10 Summary of Reproductive and Developmental Inhalation Toxicology Studies in Experimental Animals

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
Rats (male)	2 h/d for 5 wks	0, 15,080, 22,620	reproductive effects at 22,620 mg/m^3	Ono *et al.*, 1999
Rats (pregnant)	24 h/d during gestational d 9 to 14	1,500	LOAEL: 1,500 mg/m^3 for fetotoxicity	Hudak and Ungvary, 1978
Rats (pregnant)	8 h/d during gestational d 1 to 21	1,000	LOAEL: 1,000 mg/m^3 for developmental effects	Hudak and Ungvary, 1978
Mice (pregnant)	continuously during gestations d 6 to 13	0, 500, 1,500	LOAEL (mild): 500 mg/m^3 for developmental effects LOAEL (HEC): 500 mg/m^3	Hudak and Ungvary, 1978
Rats (pregnant)	6 h/d on gestational d 6 to 15	943, 2,828, 5,655, 11,310	significant increase in skeletal or visceral malformations at 943 mg/m^3	Huntingdon Research Centre, 1992a
Rats (pregnant)	6 h/d on gestational d 7 to 17	2,262, 7,540	NOAEL: 7,450 mg/m^3	Ono *et al.*, 1995
Rabbits (pregnant)	24 h/d on gestational d 7 to 20	0, 500 or 1,000	LOAEL: 500 mg/m^3 reproductive effects	Ungvary and Tatrai, 1985

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
Mice (pregnant)	24 h/d on gestational d 6 to 15	0, 500, 1,000, 1,500	LOAEL: 1,000 mg/m^3 reproductive effects LOAEL (HEC): 500 mg/m^3 for reproductive effects	Ungvary and Tatrai, 1985
Mice (pregnant)	7 h/d on gestational d 7 to 16	0, 754, 1,508	NOAEL: 1,508 mg/m^3 (for reproductive and developmental effects) NOAEL (HEC): 1,508 mg/m^3	Courtney *et al.*, 1986
Rabbits (pregnant)	6 h/d on gestational d 6 to 18	113, 377, 1,130, 1,884	no effects	Klimisch *et al.*, 1992
Rats	6 h/d, 7 d/wk , 80 d and during 15 d mating and ♀ gestational d 1 to 20 and lactation d 5 to 20	0, 377, 1,885, 7,538	NOAEL: 1,885 mg/m^3 NOAEL (HEC): 1,885 mg/m^3 based on F1 pups LOAEL: 7,538 mg/m^3 LOAEL (HEC): 7,538 mg/m^3 reproductive effects based on F1 pups	API, 1985
Rats	6 h/d, 7 d/wk, 80 d and 15 d during mating; ♀gestational d 1 to 20 and lactation d 5 to 21	0, 375, 1,875, 7,500	NOAEL: 1,875 mg/m^3 in groups where ♀rats exposed NOAEL: 7,500 mg/m^3 in groups where only ♂groups	Roberts *et al.*, 2003
Mice (pregnant)	6 h/d on gestational d 1 to 17	375, 3,750	reproductive effects	Shigeta *et al.*, 1982
Rats	6 h/d gestational d 7 until postnatal d 18	4,524	developmental and neurobehavioural effects in offspring	Hass *et al.*, 1999

4.1.5 Genotoxicity and Mutagenicity

The results of *in vivo* studies of exposed humans and *in vitro* assays with bacteria and various other test systems generally indicate that toluene is probably not mutagenic or genotoxic (ATSDR, 2000). However, the data for humans are largely inconclusive, and *in vivo* genotoxicity testing of laboratory animals is limited to a few studies that have demonstrated mixed results (ATSDR, 2000).

Richer *et al.* (1993) reported no significant effects on sister chromatid exchanges, cell cycle delay and cell mortality in human lymphocytes following exposure of five men to 50 ppm (188 mg/m^3) toluene for seven hours a day for three consecutive days, on three occasions at two week intervals. Other studies have also found no correlation between chronic occupational exposure to toluene and increased frequencies of either chromosome aberrations or sister chromatid exchanges (Haglund *et al.*, 1980; Maki-Paakkanen *et al.*, 1980). There was also no evidence of chromosomal aberrations in blood lymphocytes of workers exposed to toluene only

(Maki-Paakkanen *et al.*, 1980; Forni *et al.*, 1971), although a slight increase was detected in workers exposed to both toluene and benzene (Forni *et al.*, 1971; Funes-Craviota *et al.*, 1977). Some other studies have also reported an increased incidence of chromatid breaks, micronuclei and sister chromatid exchanges in lymphocytes of workers exposed to toluene, along with other solvent chemicals (Bauchinger *et al.*, 1982; Nise *et al.*, 1991; Pelclova *et al.*, 1990; Schmid *et al.*, 1985). Hammer *et al.* (1998) reported a concentration-related increase in sister chromatid exchange in lymphocytes of printers exposed to 141 to 328 mg/m^3 toluene (as measured by personal monitors). However, the co-exposure to other chemicals in these studies, as well as small sample sizes and limited or no historical exposure monitoring data generally confounds interpretation of these data (ATSDR, 2000).

A study of shoe workers in Bulgaria that were exposed to factory air containing 96 to 412 mg/m^3 of toluene found no exposure-related DNA damage in leukocytes, as assessed by the Comet assay (Pitarque *et al.*, 1999).

In cultured human lymphocytes exposed to toluene *in vitro*, there was no increase observed in either chromosomal aberrations or sister chromatid exchanges (Gerner-Smidt and Friedrich, 1978). Zarani *et al.* (1999) found that toluene did not induce micronuclei in human lymphocytes, with or without metabolic activation.

In vivo assays with toluene in laboratory animals have produced mixed results. Toluene was reported to induce chromosomal aberrations in the bone marrow cells of rats following inhalation exposure (Dobrokhotov and Enikeev, 1977). Toluene did not induce DNA damage in the blood, bone marrow, or liver of mice exposed to 500 ppm (1,875 mg/m^3) toluene for 6 hours a day, 5 days per week for 8 weeks (Plappert *et al.*, 1994), and also did not induce dominant lethal mutations in sperm cells of mice exposed to 400 ppm (1,500 mg/m^3) for 6 hours a day, 5 days per week for 8 weeks (API, 1981). NTP (1990) reported that toluene produced equivocal results in the mouse lymphoma assay, with and without exogenous metabolic activation. It was also reported that toluene did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells in the presence or absence of exogenous metabolic activation.

In bacterial assays, toluene was found to be non-mutagenic in reverse mutation assays with *S. typhimurium* (Mortelmans and Riccio, 1980; Nestmann *et al.*, 1980; Bos *et al.*, 1981; Litton Bionetics, Inc., 1981; Snow *et al.*, 1981) and *E. coli* (Mortelmans and Riccio, 1980), both with and without metabolic activation. NTP (1990) reported that toluene did not induce gene mutations in in *S. typhimurium* strain TA98, TA100, TA1535 or TA1537 with or without exogenous metabolic activation. Toluene did not induce mitotic gene conversion (Litton Bionetics, Inc., 1981; Mortelmans and Riccio, 1980) or mitotic crossing over (Mortelmans and Riccio, 1980) in *S. cerevisiae*.

Murata *et al.* (1999) investigated DNA damage by minor metabolites of toluene, methylhydroquinone and methylbenzoquinone, using 32P-5-end-labeled DNA fragments obtained from human genes. Formation of 8-oxo-7,8-dihydro-2-deoxyguanosine by metabolites of toluene increased in a concentration-dependent manner in the presence of Cu(II) and NADH. The authors suggest that these toluene metabolites may play a role in the expression of carcinogenicity and reproductive toxicity. Kim *et al.* (2003) reported a positive correlation between micronucleus frequency in the Tradescantia micronucleus assay and toluene concentrations in workplace air. Certain toluene metabolites, such as p-cresol, have recently been found to form DNA adducts in HL-60 cells (Gaikwad and Bodell, 2003); however, the significance of this finding to human exposure and toxicity is unclear.

4.1.6 Carcinogenicity

No association has been found between the occurrence of cancer in humans and occupational exposure to toluene. ATSDR (2000) states that available human and animal studies generally do not support a concern for the carcinogenicity of toluene.

A number of human epidemiology studies are available that assessed inhalation exposure to toluene as a possible cancer risk factor. In these studies, most cancers could not significantly be associated with toluene exposure, and there was weak consistency in the findings of those studies that did associate a particular cancer type with toluene exposure (ATSDR, 2000).

Only three cohort studies involved workers that were exposed mainly to toluene (*e.g.*, Antilla *et al.*, 1998; Svensson *et al.*, 1990; Walker *et al.*, 1993). The other available human studies evaluated workers exposed to mixtures of solvents including toluene. The information from these mixed solvent studies is inadequate to assess the carcinogenic potential of toluene, predominantly because of the lack of consistent findings across these studies, and the high likelihood of worker co-exposure to multiple other chemicals (ATSDR, 2000).

Antilla *et al.* (1998) conducted a retrospective cohort study of 5,301 workers (3,922 males and 1,379 females) monitored over the period 1973 to 1992. There was no increase in overall cancer risk, and there was no risk for cancers at specific tissue sites that were associated with exposure to toluene, except for a non-significant increase in the incidence of lung cancer in individuals exposed to toluene for more than 10 years. In this sub-group, the authors noted that workers were likely co-exposed to benzene.

Svensson *et al.* (1990) studied cancer incidence and mortality in a cohort of Swedish printers, exposed primarily to toluene, and employed for at least three months between 1925 and 1985. Worker incidence and mortality rates were compared to mortality and cancer incidence rates for the region. Current and historical monitoring data were used to estimate yearly average concentrations of toluene in workplace air. Concentrations had declined from around 450 ppm (1,689 mg/m^3) in the 1940s to around 30 ppm (113 mg/m^3) by the mid-1980s. There were indications of excess risk of morbidity and mortality for respiratory tract cancer, stomach cancer and colo-rectal cancer, but there was no significant association between increased cancer risk and cumulative exposure to toluene.

Walker *et al.* (1993) conducted a cohort mortality study of 7,814 shoe-manufacturing workers (2,529 men and 5,285 women) from two plants in Ohio. Workers were exposed to solvents and solvent-based adhesives, with toluene as the major solvent in use. An industrial hygiene survey conducted from 1977 to 1979 indicated that solvent exposure was primarily to toluene (10 to 72 ppm; 37.5 to 270 mg/m^3), but other chemicals, such as 2-butanone, acetone and hexane were recorded at similar concentrations. IARC (1999) noted that benzene might have been present as an impurity of toluene. Mortality follow up was conducted from 1940 to 1982 and relative risk estimates (SMRs) were derived using the general population of the United States as controls. While slight excess risks of lung cancer were estimated for both men and women, smoking may have been a confounding factor and relative risk of lung cancer was not found to increase with increasing duration of employment. There was also a slight excess risk for colon cancer among men and women. No other cancer types showed an excess risk in this study.

Inhalation exposure cancer bioassays with experimental animals have produced no evidence to support that toluene has carcinogenic activity.

A chronic 106-week inhalation bioassay with toluene in F344 rats of both sexes reported no carcinogenic effects (CIIT, 1980). In this study, 960 rats were exposed by inhalation for 6 hours a day, 5 days per week to 0, 30, 100 or 300 ppm (0, 113, 375, 1,125 mg/m^3) toluene. Gross and microscopic examination of tissues and organs showed no increases in neoplastic tissue or tumour masses in any exposed rats, relative to controls. However, it should be noted that this study is considered inadequate because the highest dose administered was well below the oral maximum tolerable dose for toluene, there was an unusually high incidence of lesions and pathological changes in the control rats (U.S. EPA, 1992).

A study by NTP (1990) found no increased incidences of treatment-related neoplastic lesions in either Fischer 344 rats or B6C3F1 mice exposed to toluene concentrations of 120, 600 or 1,200 ppm (450, 2,250 or 4,500 mg/m^3), for 6.5 hours a day, 5 days per week for 2 years. The NTP (1990) study is considered to be a well-conducted study that provides convincing evidence for a lack of carcinogenicity of toluene in experimental rats and mice (ATSDR, 2000). The NTP (1990) study noted that nephropathy was seen in almost all rats (including controls), and that the severity was somewhat increased in exposed rats. In one female rat, a rare renal tubular cell carcinoma was observed, and an equally rare sarcoma of the kidney was observed in another female rat exposed to 1,200 ppm. Erosion of the olfactory epithelium and degeneration of the respiratory epithelium were increased in all exposed rats. Inflammation of the nasal mucosa and metaplasia of the olfactory epithelium were increased in exposed female rats. In one female rat the 1,200 ppm group, a rare squamous cell carcinoma of the nasal mucosa was observed. In addition, squamous cell papilloma of the forestomach was observed in one female rat at 1,200 ppm, and a squamous cell carcinoma was observed in another female rat in the 1,200 ppm group. However, these rare tumours observed in few female rats were not considered exposure-related by NTP (1990). Furthermore, no exposure-related neoplasms were observed in any male rats. In mice, no biologically significant increases were observed for any non-neoplastic or neoplastic lesions (NTP, 1990).

It was therefore concluded by NTP (1990), that under the conditions of these 2-year inhalation studies, there was no evidence of carcinogenic activity for male or female F344/N rats exposed to toluene at concentrations of 600 or 1,200 ppm. There was also no evidence of toluene carcinogenicity in male or female B6C3F1 mice exposed by inhalation to concentrations of 120, 600 or 1,200 ppm for two years.

Few regulatory agencies have classified toluene as to its carcinogenicity. The U.S. EPA categorizes toluene as "D - not classifiable as to human carcinogenicity", based on no human data, a lack of appropriate animal bioassays, and mostly negative results in genotoxicity assays. Health Canada (1996) classifies toluene as Group IV – unlikely to be carcinogenic in humans.

IARC (1999) classifies toluene as Group 3 - not classifiable as to its carcinogenicity due to inadequate evidence in humans, and evidence suggesting lack of carcinogenicity in experimental animals.

4.2 Effects on Ecological Receptors

Aquatic Life

A 72 hour toluene EC50 for the alga, *Selenastrum capricornutum*, was reported to be 12.5 mg/L (Galassi *et al*., 1988). Dunstan *et al*. (1975) reported that the growth of four species of marine diatoms was reduced at toluene concentrations of >10 mg/L. However, growth was found to be stimulated in two species by <1 mg/L toluene. An eight-day EC50 for growth of *Selenastrum capricornutum* of 9.4 mg/L was reported by Herman *et al*. (1990).

A 48 hour LC50 of 11.5 mg/L was reported for *Daphnia magna* (Bobra *et al*., 1991). In freshwater fish, 96 hour LC50 values of 5.8 mg/L were reported for rainbow trout (*Oncorhynchus mykiss)* (Galassi *et al*., 1988) and 5.5 mg/L for coho salmon fry (*Oncorhynchus kisutch)* (Moles *et al*., 1981). LOEC and NOEC values for growth in coho salmon fry of 2.8 mg/L and 1.4 mg/L, respectively, were reported by Moles *et al*. (1981). Other chronic toxicity estimates for fish range from 0.02 mg/L (27 day LC50 in rainbow trout) to 68.3 mg/L (14 day LC50 in guppies) (Black *et al*., 1982; Konemann 1981).

Terrestrial Invertebrates and Microbial Processes

The no-observed-effect concentrations (NOEC) for soil microbial respiration and ammonification for toluene were reported to range from 100 to 1,300 mg/kg (Sloof and Blokzijl, 1988). The authors also reported a NOEC for nitrification of <26 mg/kg. Sloof and Blokzijl (1988) also reported that toluene impacted mortality, cocoon production and appearance in 28 day tests with the earthworm, *Eisenia foetida*. The reported NOECs ranged from 15 to 50 mg/kg, and the LC50s ranged from 150 to 280 mg/kg.

Anderson *et al*. (1991) found that 100 mg/kg of toluene in soil was not toxic to soil microorganisms. Walton *et al*. (1989) reported reduced microbial respiration at a concentration of 1,000 mg/kg toluene in soil.

Vonk *et al*. (1986) reported 14 day and 28 day LC50s in *Eisenia foetida* exposed to toluene in artificial soil. The LC50 values ranged from 100 to 180 mg/kg over both durations. NOEC values for mortality were similar. NOECs for cocoon production and appearance were 32 to 100 mg/kg and 10 to 32 mg/kg, respectively.

Toluene LC25 values for a collembolan were 521 mg/kg in coarse soil (ESG, 2002) and 406 mg/kg in fine soil (Komex, 2002). NOEC and LOEC values for the earthworm, *Eisenia andrei*, in coarse soil, were 80 and 172 mg/kg, respectively (ESG, 2002). In fine soils, the geometric mean of the NOEC and LOEC concentrations in this earthworm species was 252 mg/kg (Komex, 2002).

Plants

Chlorosis and growth inhibition may occur at toluene air concentrations of <6,000 mg/m^3, as well as >1,000 mg/kg in soil and >500 mg/L in water (CEPA, 1992). Plant growth may be stimulated at water concentrations in the range of 0.005 to 0.05 mg/L.

Currier (1951) reported that 12 mg/L toluene in water caused significant inhibition of root formation in carrots, tomatoes and barley seedlings.

ESG (2002) reported an IC25 of 234 mg/kg for reduced shoot dry mass in alfalfa exposed to toluene in coarse soil for 14 days. An IC25 of 55 mg/kg was reported for reduced root dry mass in northern wheatgrass grown in coarse soil for 14 days. Similar experiments with these two species were conducted in fine soils. In the fine soil type, an IC25 value of 120 mg/kg was reported for alfalfa (reduced shoot dry mass), and an IC25 of 112 mg/kg was reported in northern wheatgrass (reduced root wet mass)(Komex, 2002).

Other Environmental Effects

Based on the available data on the environmental fate, transport and effects of toluene, this compound is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone or alter precipitation patterns. No specific information on the photochemical smog formation potential of toluene was identified; however, it would be expected to have a similarly low to moderate smog formation potential as ethylbenzene and xylenes.

Summary

Adverse effects on the central nervous system are the critical effects of concern following acute human inhalation exposure to toluene (ATSDR, 2000). Symptoms of acute exposure progress from fatigue, headache, and decreased manual dexterity to narcosis with increasing exposure levels. Depression, memory loss, impaired coordination and reaction time also occur as exposure levels increase (ACGIH, 1992). Respiratory tract irritation is also commonly reported in acute inhalation studies with both humans and experimental animals.

Performance deficits in tests of neurobehaviour have been observed in studies with human volunteers acutely exposed to controlled toluene concentrations of >50 ppm (188 mg/m^3) and in laboratory animals repeatedly exposed to >500 ppm (1,875 mg/m^3) toluene (ATSDR, 2000). In the human volunteer studies, 50 ppm appears to be a threshold as acute exposure to toluene concentrations below 50 ppm results in few, if any, observable effects, but signs of neurological impairment have been observed with concentrations greater than 50 ppm (ATSDR, 2000). ACGIH (1992) has summarized the acute toxicity thresholds for toluene as follows. Inhalation of 100 to 200 ppm (375 to 750 mg/m^3) is associated with headaches and mild transient irritation of the upper respiratory tract; 400 ppm (1,500 mg/m^3) is associated with eye irritation, lacrimation and giddiness; 600 ppm (2,250 mg/m^3) with lethargy, giddiness and slight nausea; 800 ppm (3,000 mg/m^3) is associated with moderate to severe eye and upper respiratory tract irritation, drowsiness, nasal discharge, ataxia, dizziness and metallic taste in the mouth. In a review of the available occupational studies, ACGIH (1992) concluded that the highest toluene air concentrations that can be tolerated for short durations (3.5 to 6 hours) without measurable neurobehavioural effects were 80 to 100 ppm (300 to 375 mg/m^3).

It is well established that neurotoxicity and neurobehavioural deficits are the principal effects of long term inhalation exposure to toluene in both humans and experimental animals. Although there is a high degree of variability in the methods used, and the endpoints evaluated in the available studies, and most human studies suffer from a number of limitations, both the human and animal subchronic and chronic inhalation data generally indicate that no adverse neurological or neurobehavioural effects are likely to occur at toluene air concentrations lower than around 50 ppm (188 mg/m^3). The major symptoms following subchronic or chronic inhalation exposure to toluene in humans include subtle changes in neurological functions including cognitive and neuromuscular performance, hearing and colour discrimination in chronically exposed workers. Subchronic or chronic studies with experimental animals also indicate that major symptoms of toluene exposure include behavioural changes, hearing loss and subtle changes in brain structure, brain electrophysiology and brain chemistry. Studies of occupationally exposed workers also indicate that chronic exposure to toluene concentrations ranging from 30 to 130 ppm (113 to 488 mg/m^3) can lead to deficits in hearing and colour vision. Hearing loss has also been reported in experimental animals exposed to 700 to 1,500 ppm (2,625 to 5,625 mg/m^3) toluene (ATSDR, 2000).

There are few human studies available that investigated the reproductive or developmental effects of toluene following inhalation exposure. Overall, the human data that exists does not provide convincing evidence that toluene causes reproductive effects in humans (ATSDR, 2000). A number of developmental toxicity studies with rats, mice and rabbits exposed *via* inhalation to toluene indicate that toluene is not a potent teratogen at exposure levels below those that induce maternal toxicity, but it can retard fetal growth and skeletal development and cause behavioural alterations in offspring (ATSDR, 2000). It should also be recognized that the available developmental toxicity studies are limited by issues such as unknown or unconventional exposure durations, poorly quantified exposures, co-exposure to other solvents, inadequate descriptions of maternal toxicity, use of individual offspring instead of litters for statistical analyses, and unknown purity of toluene used (Donald *et al.*, 1991).

The results of *in vivo* studies of exposed humans and *in vitro* assays with bacteria and various other test systems generally indicate that toluene is probably not mutagenic or genotoxic (ATSDR, 2000). However, the data for humans are largely inconclusive, and *in vivo* genotoxicity testing of laboratory animals is limited to a few studies that have demonstrated mixed results (ATSDR, 2000). There is no convincing evidence that toluene has carcinogenic activity in either humans or experimental animals.

Ongoing Toxicological Research

Based on a review of current and/or ongoing research and/or assessment activities or programs overseen by Health Canada, Environment Canada, Canadian Council of Ministers of the Environment (CCME), U.S. National Toxicology Program (NTP), U.S. National Institute of Health CRISP Database, U.S. National Institutes of Environmental Health Sciences (NIEHS), various U.S. EPA offices and programs (*e.g.*, TSCA, Science Advisory Board reports, etc.), Chemical Industries Institute of Toxicology (CIIT), Toxicology Excellence for Risk Assessment (TERA), World Health Organization (WHO), Agency for Toxic Substances and Disease Registry (ATSDR) and Health Effects Institute (HEI), there appear to be a number of current or ongoing studies or reviews related to toluene toxicology under the direction of these agencies and institutes. For example, there are a number of ongoing research activities registered in the NIH CRISP (2004) database, that relate to solvent abuse of toluene, dosimetry, neurotoxicity, biomarkers, reproductive and developmental toxicity, metabolism, and ototoxicity. In addition, the U.S. EPA IRIS website indicates that toluene is presently being reassessed under the IRIS Program.

5.0 AMBIENT MONITORING METHODS

This section assesses the various air monitoring methodologies to measure toluene in ambient air, and describes their advantages and disadvantages.

5.1 Background

5.1.1 Introduction

Air monitoring is used to determine the concentrations of chemical species in the atmosphere. For any single chemical species, there are typically several methods that can be used, with varying detection levels, sampling periods/frequencies and operational levels-of-effort. Specific air monitoring methods include continuous, integrated passive, grab sampling and integrated active (Lodge, 1988). Many factors must be considered in selecting the best approach based on the overall objectives of the monitoring program. Considerations include minimum detection levels, measurement precision, averaging period and cost.

5.1.2 General Monitoring Approaches

In continuous monitors, a sample of air is drawn past a fast response detector using a pump. The detector produces an electrical signal that is proportional to the concentration of a specific chemical compound. Hourly average concentration information can be recorded by a digital data collection system (*i.e.*, a computer) or other storage medium (chart recorder).

In integrated passive sampling, a reactive surface in a controlled diffusion path is exposed for a nominal period ranging from 24 hours to one month. The reactive surface is analyzed in a chemical laboratory to determine the concentration of the captured compounds. The method is termed passive because pumps are not drawing an air sample past a detector or through a collection medium.

In grab sampling, a whole air sample is collected in a non-reactive steel canister or plastic bag. The air sample is then analyzed in a laboratory to determine the concentration of the compounds in the air sample. Grab samples typically represent samples collected over the course of a few minutes to several hours.

In integrated active sampling, a known volume of air is drawn through a column filled with an absorbent material (for gases) or a collection filter (for particles) using a pump. These absorbent columns or filters are then analyzed in a laboratory to determine the concentrations of the collected compounds. Integrated samples are typically collected once every six days for a 24-hour period.

Integrated samplers require a sorbent to entrap the chemical species being sampled. The selection of the sorbent will depend on the specific compounds being sampled. Commonly used sorbents include, but are not limited to, Tenax, XAD-2, activated charcoal, Carbotrap C, Anasorb 747, Carbosieve, or a multi-stage combination using more than one sorbent. Dewulf and Langenhove (1997) describe four criteria that can be used in the selection of an appropriate sorbent. First, it is important that the sampled compounds do not break through the sorbent and that the specific retention volume of the sorbent is known. Second, the sorbent cannot influence the sample by causing unwanted reactions with the sample. Third, it is imperative that the sorbent not be contaminated prior to, and after the sampling process. Lastly, the retention of water on the sorbent should be small to avoid any interference with the laboratory analysis of the sample.

5.1.3 Laboratory Analysis

Collected samples (grab sampling) or sample media (integrated sampling) are analyzed to determine the respective concentrations. The most common process uses a gas chromatograph (GC) coupled to an appropriate detector. The GC process requires the sample to be placed in a heated chamber and purged with inert gas (*e.g.* helium) to separate and transfer the VOC sample from the sorbent, through a cold trap, onto the front of the GC column, which is initially at a low temperature. The GC column is heated to elute individual compounds based on their retention time (Lodge, 1988). Based on the required specificity and sensitivity of the application, there are several specific and non-specific detectors that can be used.

Non-specific detectors include the nitrogen-phosphorous detector (NPD), the flame ionization detector (FID), the electron capture detector (ECD) and the photo-ionization detector (PID) (U.S. EPA, 1999a). These detectors are generally less costly per analysis than specific detectors and can be more sensitive for specific classes of compounds. For example, if multiple halogenated compounds are targeted, the ECD would provide more accurate identification. The non-specific detectors are coupled to the GC and individual compounds are identified by their retention time. The downside of using non-specific detectors is that they are prone to greater margins of error since they rely on retention times alone for compound identification. Also, there is a chance that interference can occur due to non-targeted compounds (U.S. EPA, 1999a).

Specific detectors include the linear quadrupole mass spectrometer (MS) and the ion trap detector. Both of these detectors are mass spectrometers. The mass spectra for individual peaks in the ion chromatogram are analyzed for the fragmented mass patterns of the primary and secondary ions. These fragmentations are compared to known spectra observed under like conditions. Based on the GC retention time and the mass spectral characteristics, each VOC in the sample can be determined.

Mass spectrometry is a more accurate method of determining specific compounds in ambient air samples because of their range of precision and simple identification process. Although the non-specific detectors have some advantages such as lower cost and higher sensitivity, the U.S. EPA (1999b) stresses that mass spectrometry is considered a more definitive identification technique and reduces the chances of misidentification.

5.1.4 Information Sources

Standardized air monitoring methods are documented by the U.S. Environmental Protection Agency (U.S. EPA), the Occupational Safety and Health Administration (OSHA) and the National Institute of Occupational Safety and Health (NIOSH). These agencies provide detailed approaches required to adequately measure hazardous air pollutants (HAPs) in ambient and workplace air using a variety of air monitors and analysis techniques. Other information sources (*e.g.* technical journals, conference proceedings) were also reviewed to explore other air monitoring technologies, as well as new or emerging technologies.

5.1.4.1 U.S. EPA

The U.S. EPA has developed several air toxics methodologies for sampling VOC in ambient air. Detailed descriptions of these methods are available on the U.S. EPA Technology Transfer Network (TTN) – Ambient Monitoring Technology Information Center (AMTIC). The following U.S. EPA air toxics methods can be used to sample toluene:

- Method TO-1: Method for the determination of volatile organic compounds in ambient air using Tenax adsorption and gas chromatography/mass spectrometry (GC/MS) (U.S. EPA, 1984a).
- Method TO-2: Method for the determination of volatile organic compounds in ambient air by carbon molecular sieve adsorption and gas chromatography/mass spectrometry (GC/MS) (U.S. EPA, 1984b).
- Compendium Method TO-14A: Determination of volatile organic compounds in ambient air using specially prepared canisters with subsequent analysis by gas chromatography (GC) (U.S. EPA, 1999a).
- Compendium Method TO-15A: Determination of volatile organic compounds in air collected in specially-prepared canisters and analyzed by gas chromatography/mass spectrometry (GC/MS) (U.S. EPA, 1999b).
- Compendium Method TO-17: Determination of volatile organic compounds in ambient air using active sampling onto sorbent tubes (U.S. EPA, 1999c).

The following methods provide alternative monitoring techniques that are specific to point source monitoring:

- Method 0030: Volatile Organic Sampling Train (VOST). (U.S. EPA, 1986).
- Method 0031: Sampling Method for Volatile Organic Compounds (SMVOC) (U.S. EPA, 1996a).
- Method 0040: Sampling of Principal Organic Hazardous Constituents from Combustion Sources using Tedlar Bags (U.S. EPA, 1996b).

Each of these methodologies can be applied to a range of VOC as determined by previously successful trials conducted by the U.S. EPA. All eight methods can be used to sample and analyze toluene. The following sections describe each U.S. EPA method.

U.S. EPA Method TO-1

Method TO-1 is limited to non-polar organic compounds that have a boiling point between 80° and 200°C. The U.S. EPA provides a list of compounds that can be sampled using this method as not all non-polar organic compounds within that boiling range can be determined. Toluene is among those compounds that can be determined.

This method uses sorbent tubes to trap VOC in ambient air. The ambient air to be sampled is drawn through a chamber containing Tenax (poly 2,6-Diphenyl phenylene oxide) sorbent. The toluene adheres to the Tenax sorbent while other highly volatile organic compounds, and most inorganic components pass through the chamber. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

U.S. EPA Method TO-2

Method TO-2 is limited to non-polar and non-reactive organic compounds that have a boiling point between −15 and 120°C. The U.S. EPA provides a list of compounds that can be sampled using this method as not all non-polar and non-reactive organic compounds within that boiling range can be determined. Toluene is among those compounds that can be determined.

This method is based on a carbon molecular sieve (CMS) adsorption process. The ambient air to be sampled is drawn through a chamber containing the CMS sorbent. The toluene adheres to the CMS sorbent while other highly volatile organic compounds, and most inorganic components pass through the chamber. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

U.S. EPA Compendium Method TO-14A

Method TO-14A provides procedures for sampling VOC in pressurized (above atmospheric pressure) and subatmospheric pressure (below atmospheric pressure) canisters. Originally, this method was based on the collection of whole ambient samples using SUMMA passivated stainless steel canisters but can now be applied to other types of canisters. It can be applied to ambient concentrations of VOC above 0.5 ppbv and will usually require a sample size on the order of one litre. The U.S. EPA provides a list of compounds that can be sampled based on their storage capability in canisters. Toluene is among those compounds that can be determined.

This method uses an empty canister and pump-ventilated sample line for sample collection. For pressurized sampling, an additional pump to pressurize the canister is required. The ambient air sample is drawn through a sampling train, which is made up of components that regulate the rate and length of sampling, into the specially prepared passivated canister. The sample is transferred to a laboratory for analysis with a GC coupled to one of many GC detectors described in Section 5.1.4.

U.S. EPA Compendium Method TO-15A

Method TO-15A is an extension of the sampling method TO-14A. This method is more generalized but provides better definitions for VOC sampling methods. The set of compounds that can be sampled using the specially prepared canisters is a subset of the 97 VOCs that are listed as hazardous air pollutants in the 1990 amendments of the U.S. Clean Air Act, and includes toluene. This list includes more compounds than are described in Method TO-14A. The only means of laboratory analysis for this method is by GC/MS. Furthermore, Method TO-15A includes more detailed guidelines for quality control, mainly internal analytical standards and frequent verification of analytical performance.

U.S. EPA Compendium Method TO-17

Method TO-17 is a thermal desorption based ambient air monitoring method for VOC and is applicable for 0.5 and 0.25 ppbv ambient concentration levels. The U.S. EPA provides a list of compounds for which this method can be used based on sampling performance. These compounds, which are the same as those that can be sampled using TO-15A, are a subset of the 97 VOCs that are listed as hazardous air pollutants in the 1990 amendments of the U.S. Clean Air Act. Toluene is among those compounds that can be determined.

This method uses single or multi sorbents packed in tubes in order of increasing sorbent strength, allowing for a wide volatility range of VOC to be sampled. Using multi-sorbent tubes, compounds with higher molecular weights are retained first, and compounds with lower molecular weights last. If a single sorbent is being used, it should be specific to the target compound. Because of the specificity of certain sorbents, the thermal desorption process is very efficient.

The sample is drawn through a tube containing the selected sorbents. The toluene adsorbs to the sorbents while unwanted VOC and most other inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

U.S. EPA Method 0030

Method 0030 was developed for sampling volatile principal organic hazardous constituents (POHC) from the stack gas effluents of hazardous waste incinerators. Alberta Environment has developed a similar stack sampling code (AE, 1995) that describes in detail methods for sampling VOC (method 25) in stack gas effluent. Volatile POHC are compounds with boiling points that are less than 100°C. The U.S. EPA provides a list of compounds for which this method can be used. Toluene is among those compounds that can be determined.

This method employs a 20 litre sample stack gas effluent which contains volatile POHC. Using a glass-lined probe and a volatile organic sampling train (VOST), the gas is withdrawn at a rate of 1 L/min. The stream is then cooled to 20°C as it passes through a water-cooled condenser. The volatile POHC are collected on a pair of resin traps. The first trap contains Tenax (see U.S EPA Method TO-1) while the second contains a mixture of Tenax and petroleum-based charcoal. Up to six pairs of sorbent traps can be used to collect the volatile POHC over a period of two hours. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

U.S. EPA Method 0031

Method 0031 was developed for sampling and analyzing VOC in gaseous emissions from stationary sources including hazardous waste incinerators. This method is limited to VOC that have a boiling point between -15 and 120°C. The U.S. EPA provides a list of compounds for which this method can be used based on sampling performance.

This method employs a sampling module and meter box to withdraw a 20 litre sample of effluent gas which contains VOC. Using a heated glass-lined probe and a sampling method for volatile organic compounds (SMVOC) train, the gas is withdrawn at a rate of 1 L/min. The stream is then cooled to 20°C as it passes through a water-cooled condenser. The VOC are collected in an impinger placed between two Tenax (see U.S EPA Method TO-1) traps and an Anasorb-747 trap. Up to six pairs of sorbent traps can be used to collect the volatile POHC over a period of two hours. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

U.S. EPA Method 0040

Method 0040 was developed for sampling and analyzing VOC in gaseous emissions from stationary sources such as hazardous waste incinerators using Tedlar bags. This method is limited to VOC that have a boiling point less than 121°C. A study by Rao *et al.* (1997) conducted in Bombay, India employed Tedlar bags for sampling ambient air at a height of 3 m above ground level. This shows the diversity of this sampling technique in that it is not limited to stack sampling. The U.S. EPA provides a list of compounds for which this method can be used based on sampling performance.

This method employs a heated probe and filter through which the sample is drawn before entering a heated 3-way valve leading to a condenser where moisture and condensate are removed from the stream to a trap. The VOC are collected in a Tedlar bag that is held in a rigid, air-tight container. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

5.1.4.2 NIOSH

NIOSH has developed several air toxics methodologies for sampling VOC in workplace air. Detailed descriptions of these methods are contained in the NIOSH Manual of Analytical Methods (NMAM). It should be noted that the NMAM was intended to achieve consistent industrial hygiene analyses and was not designed specifically for ambient air. The following NIOSH analytical method can be used to sample toluene:

- NIOSH Manual of Analytical Methods, Fourth Edition, Method 1500: Hydrocarbons, 36 – 126°C BP (NIOSH 1994a).
- NIOSH Manual of Analytical Methods, Fourth Edition, Method 4000: Toluene (diffusive sampler) (NIOSH 1994b).

Method 1500 can be applied to a range of organic compounds whereas Method 4000 is limited to toluene. Method 1500 is a general sampling method and provides a list of compounds that can be determined. NIOSH provides methods for individual and grouped compounds. For example, Method 4000 describes a specific sampling method for toluene. The following sections describe both NIOSH methods.

NIOSH Method 1500

Method 1500 employs an activated charcoal (prepared from coconut shells) based solid sorbent tube, which is a commonly used sorbent because of its reactive surface which promotes higher adsorptive capacity. It also has a very high area to weight ratio which allows for higher sampling capacity. This method is limited to VOC that have a boiling point between 36 and 126°C. Toluene is among those compounds that can be determined.

The sample is drawn through a tube containing the activated charcoal sorbent. The toluene would adsorb to the charcoal sorbent while other highly volatile organic compounds and most inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

NIOSH Method 4000

Method 4000 employs a diffusive sampler for collecting toluene samples. The 3M 3500 passive sampler does not require that the collection element be transferred with the sample while other samplers such as the Gilian Trace Air OVM-1/OVM-2 do require that the sorbent pad be collected in a sealed vial. A third type of passive sampler that can be used for this application is the Draeger ORSA-5 passive sampler which uses a granular sorbent rather than a collection element.

The passive samplers will usually use activated charcoal collection elements. The air to be sampled is drawn through a mesh screen and through the desorption solvent chamber. The sample is collected on the collection element. Hydrogen disulphide is added to each sample as an eluent. The sample is then transferred to a laboratory for analysis with a GC coupled to a FID.

5.1.4.3 OSHA

OSHA has developed several air toxics methodologies for sampling VOCs in ambient air. Detailed descriptions of these methods are available from the Directorate of Science, Technology and Medicine (DSTM): Salt Lake Technical Center (SLTC). It should be noted that these methods were intended to provide a uniform and practical means for evaluating workplace air quality and were not designed specifically for ambient air. The following OSHA analytical methods can be used to sample toluene:

- OSHA Sampling and Analytical Methods, Organic Method 7: Organic Vapours (OSHA, 2000).
- OSHA Sampling and Analytical Methods, Organic Method 111: Toluene (OSHA, 1999).

Organic Method 7 can be applied to a range of organic compounds whereas Organic Method 111 is limited to toluene. Organic Method 7 is a general sampling method and provides a list of compounds that can be determined. OSHA usually provides sampling methods for individual and grouped compounds. For example, Method 111 describes a specific sampling method for toluene. The following sections describe both OSHA methods.

OSHA Method 7

Method 7 is a general organic vapour sampling methodology. It uses an activated charcoal based solid sorbent tube similar to that described in NIOSH Method 1500. Activated charcoal (prepared from coconut shells) is a commonly used sorbent because its reactive surface promotes higher adsorptive capacity. It also has a very high area to weight ratio which allows for higher sampling capacity.

The sample is drawn through a tube containing activated charcoal sorbent. The toluene adsorbs to the charcoal sorbent while other highly volatile organic compounds and most inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

OSHA Method 111

Method 111 describes two possible ways to sample toluene. The first method is similar to Method 7; using either an activated charcoal sorbent or Anasorb-747 as the collection medium and *N,N*-dimethylformamide/carbon disulphide as the desorption solvent.

Another method for sampling toluene is through diffusive sampling. This passive sampling technique uses either the SKC 575-002 passive sampler or the 3M 3520 Organic Vapour Monitor. The passive samplers can be very small, and can be affixed to a worker's collar. Since OSHA is primarily interested with workplace safety, they suggest that the monitor should be placed near the breathing area (*i.e.* mouth and nose). The ambient air to be sampled is drawn through glass tubes packed with mesh activated charcoal. The sample is desorbed using a *N,N*-dimethylformamide/carbon disulphide desorption solvent. The sample is then transferred to a laboratory for analysis with a GC coupled to a FID.

5.1.4.4 Alternative and Emerging Technologies

The combination of the U.S. EPA, NIOSH, and OSHA ambient air sampling methods provides a broad scope of approaches. The sampling methods described in this section are designed for use over an 8-h to 24-h period. There are, however, other notable methods of sampling toluene that have been used in the past for specific applications.

Kuo *et al.* (2000) sampled the road-side concentrations of certain VOC including toluene in Taichung, Taiwan. Their methodology was a similar approach as U.S. EPA Compendium TO-17, NIOSH method 1501, and OSHA method 7. A small stainless steel tube containing a Carbopack B sorbent and a low-flow sampling pump was attached to the collar of motorists. A GC coupled to a MS was used for analysis of samples.

Uchiyama *et al.* (1999) successfully used a modified diffusion sampler with thermal desorption for analysis since higher sensitivity was required for their application. The diffusive sampler used either Carboxen or Carbotrap B sorbents to collect VOC through the molecular diffusion and collection. A GC coupled to a MS was used for analysis of samples.

Leibrock and Slemr (1997) conducted a fairly unique, yet effective, sampling technique without the use of a sorbent. Their sampler design employed two cryogenic sampling traps that would remove compounds from the ambient air being drawn into the sampler dependant on their temperature resistance. A GC coupled to a MS was used for analysis of samples.

Environment Canada has used SUMMA canisters based on the U.S. EPA Compendium TO-14A to measure for urban pollutants. This method has also been used in Edmonton, Alberta (Cheng *et al.*, 1997) to measure the concentration of VOC (including toluene) in ambient air.

For long-term exposure trends, passive diffusion monitors such 3M 3500 Organic Vapour Monitors have been used. Usually these monitors are exposed for 7 to 24 days and returned to a laboratory for analysis. In a recent animal health study, these monitors were used to measure VOC concentrations in rural Alberta, Saskatchewan and British Columbia.

As new and emerging technologies are developed, agencies such as the U.S. EPA provide information to users ensuring that the best available environmental practices are upheld.

6.0 EXISTING AMBIENT GUIDELINES

Current recommended or proposed toluene ambient air quality guidelines from selected regulatory agencies in Canada (other than Alberta), the United States and elsewhere are summarized in Table 11. Appendix A contains further information on each of these existing guideline values.

In general, all jurisdictions reviewed have common uses for their ambient air quality guidelines, including:

- Reviewing permit applications for air emission sources
- Investigating accidental releases or community complaints about adverse air quality for the purpose of determining follow-up or enforcement activity
- Conducting health risk assessments of industrial facilities and airsheds
- Monitoring and controlling ambient air quality

The development of ambient air quality guidelines is driven by numerous societal and scientific issues, which require consideration of numerous factors such as aesthetics, property damage, toxicology and ecology. Odour, for example, is an issue of aesthetics, and for chemicals with particularly distasteful odours, guideline values may be driven by odour thresholds, while for airborne chemicals that are corrosive, damage to structures may be a key consideration.

In terms of toxicology, air quality guidelines typically consider basic toxicological principles, which dictate that the response of an organism is a function of the magnitude of the dose and the duration over which the dose is received. The nature of the response of organisms (*i.e.*, the target tissues or organs and the toxicological endpoints) is another important consideration. For example, chemicals that act as primary respiratory irritants may have guidelines developed that are protective of these types of effects. Where toxicity concerns relate to non-respiratory targets (*e.g.*, liver or kidney) or to toxicological endpoints of late onset (*e.g.*, cancer, reproductive), air quality guidelines may be established to be protective of these types of effects. Chemicals that have multiple toxicological endpoints in more than one tissue or organ may have guidelines developed that are protective of the most sensitive toxic effects. Another consideration is the estimated or actual degree of exposure of key receptors to the air pollutant, particularly receptor groups that may exhibit sensitivity to the air pollutant (*e.g.*, elderly, asthmatics, children, *etc.*). Other important considerations in establishing an air quality guideline include the available technologies (and their costs) for routinely or periodically monitoring for the pollutant in air, and the availability and technical feasibility of approaches for estimating ambient ground-level air concentrations, in order to compare to air quality guidelines.

The three most common approaches by which ambient air quality guidelines are developed are as follows:

1. Using an occupational exposure level (OEL) and dividing it by safety or uncertainty factor, and amortizing for continuous exposure. These factors are intended to account for differences between eight-hour exposures in the workplace and continuous 24-hour environmental exposures, increased susceptibility of individuals in the general population

versus the relatively healthy worker, and uncertainties in the margin of safety provided in an occupational exposure limit. It should be recognized however, that the use of OEL values has its limitations. For example:

- OELs are based on human effects information in industrial settings and may not accurately reflect ambient environmental exposure situations.
- OELs are derived to be protective of workers who are typically considered in good health and within the age range of 18 to 65 years. Such individuals are potentially less sensitive and/or susceptible to the effects of airborne pollutants than members of the general population. Among the general populations, there may be subpopulations or individuals that are more sensitive or susceptible to the effects of an airborne pollutant (*e.g.*, elderly, young children, asthmatics, people with pre-existing respiratory conditions, etc.)
- Worker exposures are typically based on a normal work schedule (eight hours per day, five days per week). For this work schedule, there are two days per week (weekends) in which the body may eliminate much of the accumulated substances before the next workweek begins. However, for individuals continuously exposed to an air pollutant in the ambient environment, there is no similar period of no exposure.
- For these reasons, agencies using OELs as the basis for ambient air quality guidelines typically adjust OELs by applying safety or uncertainty factors.

2. Threshold chemical risk assessment procedures: Used for chemicals that are not believed to act as carcinogens and that exhibit a clear toxicity threshold. In this approach, a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) from a suitable animal or human study is divided by a series of uncertainty factors that account for issues such as: differences between animals and humans, sensitive individuals, use of a LOAEL instead of a NOAEL, and for extrapolation from subchronic to chronic exposure durations.

3. Non-threshold chemical risk assessment procedures: Used for substances believed act as carcinogens. Cancer potency estimates, slope factors, tumorigenic potency values, etc. are used to establish ambient air levels based on acceptable levels of incremental lifetime cancer risk, such as one in 100,000. These acceptable levels are established by regulatory agencies.

Finally, the potential ecological impacts of airborne chemicals are also important considerations in the guideline-setting process. Although a chemical may have no direct impact on human health or property, transfer of the chemical from the air to the terrestrial and aquatic environments by dry or wet deposition could have ecological impacts, depending on the physical and chemical properties of the substance.

Current occupational exposure limits for toluene derived by ACGIH, NIOSH and OSHA are based on human studies where central nervous system (CNS) toxicity and irritant effects were demonstrated at air concentrations above 40 ppm (150 mg/m^3) (ACGIH, 1992). The current ACGIH TLV-TWA is 50 ppm (188 mg/m^3). ACGIH has also assigned a skin designation for toluene. No STEL has been derived by ACGIH. The TLV-TWA is considered protective of CNS, irritant and human reproductive effects (ACGIH, 1992). The OSHA PEL-TWA and NIOSH REL values are 100 ppm (375 mg/m^3). Short-term or ceiling exposure levels have also been established for toluene by these two agencies. The current STEL values from OSHA and NIOSH are 150 ppm (563 mg/m^3). ACGIH (1992) reports that occupational exposure limits from other countries are similar. For example, Australia and Germany use a threshold value of 100 ppm (375 mg/m^3), while Sweden uses a threshold of 80 ppm (300 mg/m^3), and the U.K. uses a threshold of 50 ppm (188 mg/m^3). Australia and the U.K. use a STEL of 150 ppm (563 mg/m^3). Germany uses a short-term level of 500 ppm (1,875 mg/m^3). Sweden uses a 15-minute short-term value of 100 ppm (375 mg/m^3).

NIOSH (2004) reports an immediately-dangerous-to-life-and-health (IDLH) value of 500 ppm (1,875 mg/m^3). The IDLH is based on acute inhalation toxicity data in humans reported in Gamberale and Hultengren (1972); von Oettingen *et al.* (1942); and Wilson (1943). An IDHL would not typically be considered as an appropriate basis for an ambient air quality guideline.

A number of agencies have derived health-based airborne ambient exposure levels for toluene that are based on relatively recent reviews of the toxicological literature, including the U.S. EPA, ATSDR, CalEPA OEHHA and Health Canada. The toluene limits from these agencies are described below.

The current U.S. EPA (1992) RfC value for toluene is 0.4 mg/m^3. Principal studies considered for RfC derivation were Foo *et al.* (1990) for CNS effects in humans, and NTP (1990) for nasal irritant effects in rats. As the CNS effect was judged to be a more severe and relevant endpoint, the LOAEL from Foo *et al.* (1990) was used to derive the RfC. The RfC is based on neurological effects in humans reported in Foo *et al.* (1990), who identified a LOAEL of 88 ppm (332 mg/m^3), which the U.S. EPA converted to a LOAEL (HEC) of 119 mg/m^3. A cumulative uncertainty factor of 300 was applied to this LOAEL (HEC) to yield the RfC [10 for intraspecies variability; 10 for the use of a LOAEL; 3 for database deficiencies, including the lack of well-characterized laboratory animal exposures evaluating neurotoxicity and respiratory irritation]. The U.S. EPA assigns a medium confidence rating to the RfC as long-term data in humans are not available for neurotoxicity or irritation endpoints, and the available reproductive/developmental studies were not considered adequately comprehensive.

The CalEPA OEHHA (1999) derived an acute one-hour REL of 9.8 ppm (37 mg/m^3). This REL was based on the six-hour study by Andersen *et al.* (1983) where the critical effects were impaired reaction time, headache, dizziness, a feeling of intoxication and slight eye and nose irritation. This study identified a LOAEL of 100 ppm and NOAEL of 40 ppm. Based on the NOAEL, the OEHHA extrapolated a one-hour concentration of 98 ppm. A cumulative uncertainty factor of 10 (for intraspecies differences) was then applied to yield the acute REL. OEHHA (1999) also developed an airborne level of toluene that is protective against severe adverse effects (*i.e.*, 5 ppm; 19 mg/m^3 over a six-hour duration). This value was based on a NOAEL of 500 ppm for fetotoxicity reported in IRDC (1985). An uncertainty factor of 100 was applied to the NOAEL to account for animal to human extrapolation and for intraindividual variability (10-fold each).

OEHHA (2003) derived a chronic REL for toluene of 0.07 ppm (0.3 mg/m^3). The REL was derived based on the rat study by Hillefors-Berglund *et al.* (1995) and is supported by the human studies of Orbaek and Nise (1989) and Foo *et al.* (1990). The critical effects were decreased brain weight, and altered dopamine receptor binding in rats exposed for 6 hours a day, 5 days per week for 4 weeks. A LOAEL and NOAEL of 80 ppm and 40 ppm, respectively were reported by Hillefors-Berglund *et al.* (1995). The NOAEL was duration adjusted [40 ppm x 6/24 x 5/7] to represent continuous exposure, which yielded an adjusted value of 7 ppm (26 mg/m^3). This was also considered representative of HEC concentration by OEHHA. A cumulative uncertainty factor of 100 was then applied [10 for subchronic study duration; 10 for intraspecies differences] to yield the chronic REL. No interspecies uncertainty factor was considered necessary as a similar LOAEL was reported in the human study by Foo *et al.* (1990).

ATSDR (2000) derived an acute (≤14 days) MRL of 1 ppm (3.75 mg/m^3). This MRL is based on the study by Andersen *et al.* (1983) in which 16 healthy young subjects with no previous exposure to organic solvents were exposed to toluene 6 hours a day over 4 consecutive days. The test concentrations were 0, 10, 40 or 100 ppm. There was a statistically significant increase in the occurrence of headaches, dizziness, and feelings of intoxication at 100 ppm. No adverse effects were reported at the 10 and 40 ppm levels. A NOAEL of 40 ppm was identified, which was adjusted for continuous exposure [NOAEL x 8/24 x 5/7]and then divided by an uncertainty factor of 10 (for human variability) to yield the acute MRL. No MRL has been derived for intermediate-duration (15–364 days) inhalation exposure to toluene; however ATSDR (2000) did derive a chronic MRL (>365 days) which is believed to be protective of intermediate duration exposures as well.

The ATSDR (2000) chronic MRL is 0.08 ppm (0.3 mg/m^3). It is based on a LOAEL of 35 ppm toluene for colour vision impairment in shoemakers reported by Zavalic *et al.* (1998a). This LOAEL was adjusted for continuous exposure [LOAEL x 8/24 x 5/7] and an uncertainty factor of 100 (10 for the use of a LOAEL; 10 to account for human variability) was applied to yield the chronic MRL.

Health Canada (Meek and Chan, 1994; Health Canada, 1996) reports a tolerable concentration (TC) for toluene of 3.75 mg/m^3 that is based on a NOAEL of 150 mg/m^3 observed in the study by Andersen *et al.* (1983). This study noted neurological deficits as measured by a variety of tests, an increase in neurological symptoms and irritation of the respiratory tract following exposure of 16 volunteers to 375 mg/m^3 toluene for 6 hours a day over 4 days. These effects became increasingly severe and persistent with increasing concentration and/or duration of exposure, but were reversible upon cessation of exposure. No adverse effects were observed at 150 mg/m^3. A factor of 6/24 was applied to convert the NOAEL to a continuous exposure, and an uncertainty factor of 10 was then applied (for intraspecies variation), to yield the TC of 3.75 mg/m^3. TERA-ITER (2004) notes that the Health Canada value was derived before several newer studies were completed.

For the most part, the guidelines presented below in Table 11 are derived based on the U.S. EPA RfC of 0.4 mg/m^3, the ACGIH TLV-TWA values of 50 ppm (188 mg/m^3) or the NIOSH REL-TWA value of 100 ppm (375 mg/m^3)(adjusted with various modifying and uncertainty factors). Ontario, Quebec and the World Health Organization have developed ambient air guidelines that are based upon odour effects of toluene, rather than health effects data. In the available documentation from some agencies, the basis behind the air quality guideline is not clearly specified. Further information on the scientific basis for these guidelines, the application of uncertainty factors and the practical application of these guidelines by the respective agencies, is provided in Appendix A.

Table 11 Summary of Existing Air Quality Guidelines for Toluene

Agency	Name of Guideline (Averaging Period)	Guideline Value (mg/m^3)	Basis of Guideline	Date of Guideline[a]
California Environmental Protection Agency, Office of Environmental Health Hazard Assessment	Acute REL (1 h)	37	Andersen *et al.*, 1983.	1999
	Level Protective of Severe Adverse Effects (6 h)	19	IRDC, 1985.	1999
	Chronic REL (continuous lifetime daily exposure)	0.3	Hillefors-Berglund *et al.*, 1995.	2003
Health Canada	TC (continuous lifetime daily exposure)	3.75	Andersen *et al.*, 1983.	1996
Louisiana Department of Environmental Quality	AAS (8 h)	8.9	Scientific basis not provided in available documentation.	2003
Massachusetts Department of Environmental Protection	TEL (24 h)	0.08	U.S. EPA RfC of 0.4 mg/m^3. Divided by 5 to account for exposure through media other than air.	1995
	AAL (annual)	0.02	U.S. EPA RfC of 0.4 mg/m^3 and 20-fold uncertainty factor.	
	ATC (continuous lifetime daily exposure)	0.4	U.S. EPA RfC of 0.4 mg/m^3.	
Michigan Department of Environmental Quality	ITSL (24 h)	0.4	U.S. EPA RfC of 0.4 mg/m^3.	1992
Minnesota Department of Health	Acute HRV (1 h)	37	Scientific basis not provided in available documentation, but is stated that HRVs are derived using best available peer-reviewed science and public health policies at the time of development.	2003
	Chronic HRV (annual)	0.4		
Netherlands Research for Man and Environment (RIVM)	TCA (continuous lifetime daily exposure)	0.4	U.S. EPA RfC of 0.4 mg/m^3.	2001
Newfoundland and Labrador Department of the Environment	AQS (24 h)	2.0	Scientific basis not provided in available documentation.	2003

Agency	Name of Guideline (Averaging Period)	Guideline Value (mg/m^3)	Basis of Guideline	Date of Guideline[a]
	POI (1 h)	1.6	Scientific basis not provided in available documentation.	
New Hampshire Department of Environmental Services	AAL (24 h)	0.67	ACGIH TLV-TWA of 50 ppm.	1997
	AAL (annual)	0.4	U.S. EPA RfC of 0.4 mg/m^3.	
New Jersey Department of Environmental Protection	Short term RfC (24 h)	37	CalEPA OEHHA 1 h REL	2003
	RfC (continuous lifetime daily exposure)	0.4	U.S. EPA RfC of 0.4 mg/m^3.	
New York State Department of Environmental Conservation	SGC (1 h)	37	Scientific basis not provided in available documentation. Reported to de developed independently by NYSDEC.	2000
	AGC (continuous lifetime daily exposure)	0.4	U.S. EPA RfC of 0.4 mg/m^3.	
North Carolina Department of Environment and Natural Resources	TAPG (1 h)	56	Scientific basis not provided in available documentation.	2001
	TAPG (24 h)	4.7	Scientific basis not provided in available documentation.	
Oklahoma Department of Environmental Quality	MAAC (24 h)	37.7	NIOSH REL-TWA of 100 ppm.	2003
Ontario Ministry of Environment and Energy	AAQC (24 h)	2.0	Odour effects.	2001
	POI (1/2 h)	2.0		
Quebec Ministry of the Environment	MAQC (15 minute)	1.0	30 minute odour annoyance threshold from WHO, 1999	2002
	MAAQC (continuous lifetime daily exposure)	0.4	U.S. EPA RfC of 0.4 mg/m^3.	
Texas Natural Resource Conservation Commission	Short- term ESL (1 h)	1.88	ACGIH TLV-TWA of 50 ppm.	2003
	Long-term ESL (annual)	0.19	ACGIH TLV-TWA of 50 ppm.	
U.S. Agency for Toxic Substances and Disease Registry	Acute MRL (1-14 days)	3.76	Andersen *et al.*, 1983	2000
	Chronic MRL (>365 days)	0.3	Zavalic *et al.*, 1998a	
U.S. Environmental	RfC (continuous lifetime	0.4	Foo *et al.*, 1990.	1992

Agency	Name of Guideline (Averaging Period)	Guideline Value (mg/m^3)	Basis of Guideline	Date of Guideline[a]
Protection Agency, Integrated Risk Information System (IRIS)	daily exposure)			
Vermont Agency of Natural Resources	HAAS (24 h)	8.9	NIOSH REL-TWA of 100 ppm.	2001
Washington Department of Ecology	ASIL (24 h)	0.4	U.S. EPA RfC of 0.4 mg/m^3.	1998
World Health Organization	30 minute GV	1.0	Odour threshold.	1999
	GV (1 week)	0.26	Available documentation specifies basis is a LOAEL of 332 mg/m^3 for neurological effects in workers adjusted for duration and with uncertainty factors applied.	

a Date guideline was either promulgated or date of last review/revision by agency.

The air quality guideline values used by the jurisdictions listed in Table 11 can be split into short-term and long-term values. Short-term ambient air guidelines for toluene include 15-minute, half-hour, one-hour, six hour, eight-hour and 24-hour averaging periods. Only Quebec has a 15 minute value (1.0 mg/m^3). Ontario and the WHO cite half-hour limits (2.0 and 1.0 mg/m^3, respectively). One-hour limits exist in California, Minnesota, Newfoundland and Labrador, New York, North Carolina and Texas. The lowest one-hour guideline is 1.6 mg/m^3 (Newfoundland and Labrador), while the highest is 56.0 mg/m^3 (North Carolina). Only California cites a six-hour guideline value (19 mg/m^3), while only Louisiana cites an eight-hour limit (8.9 mg/m^3). Twenty-four hour guidelines exist in Massachusetts, Michigan, Newfoundland and Labrador, New Hampshire, New Jersey, North Carolina, Oklahoma, Ontario, Vermont and Washington. These 24-hour guideline values range from 0.08 mg/m^3 (Massachusetts) to 37.7 mg/m^3 (Oklahoma). Long-term air quality guidelines in the jurisdictions reviewed are generally listed as annual ambient limits or are stipulated for continuous lifetime daily exposure. Such limits exist within California, from Health Canada, Massachusetts, Minnesota, The Netherlands, New Hampshire, New Jersey, New York, Quebec, Texas and the U.S. EPA. These values range from 0.02 mg/m^3 (Massachusetts) to 3.75 mg/m^3 (Health Canada), with the majority of these jurisdictions using the U.S. EPA RfC of 0.4 mg/m^3 as the basis for annual or continuous lifetime daily exposure guidelines. ATSDR developed an acute MRL (1 to 14 days) of 3.76 mg/m^3 and a chronic MRL (>365 days) of 0.3 mg/m^3. The WHO derived a one-week guideline value of 0.26 mg/m^3.

It should be noted that the considerable variability observed between guidelines is primarily the result of differences in the approaches used in their derivation. While there is generally good agreement with respect to the choice of toxicological studies and data used as the basis for the guidelines, all jurisdictions use different averaging periods and apply unique sets of uncertainty and modifying factors and assumptions in guideline development. The decision to use a particular approach involves policy decisions in addition to scientific considerations.

7.0 DISCUSSION

Toluene is not corrosive. While it is highly flammable, this is a safety issue that is separate and distinct from health-based guideline development.

Few regulatory agencies have classified toluene as to its carcinogenicity. The U.S. EPA categorizes toluene as "D - not classifiable as to human carcinogenicity", based on no human data, a lack of appropriate animal bioassays, and mostly negative results in genotoxicity assays. Health Canada (1996) classifies toluene as Group IV – unlikely to be carcinogenic in humans. IARC (1999) classifies toluene as Group 3 - not classifiable as to its carcinogenicity due to inadequate evidence in humans, and evidence suggesting lack of carcinogenicity in laboratory animals. Furthermore, there are currently no existing ambient air quality guidelines or other health-based airborne exposure limits for toluene that are based on carcinogenic effects. The results of *in vivo* studies of exposed humans and *in vitro* assays with bacteria and various other test systems generally indicate that toluene is probably not mutagenic or genotoxic (ATSDR, 2000). Based on these considerations, toxicological considerations for toluene should focus on non-cancer endpoints following acute and chronic exposure.

Review of the physical chemical properties (Section 2.0) and the toxicology (Section 4.0) of toluene indicate several key benchmark air concentrations and associated effects that should be considered in establishing an ambient air quality guideline. Odour thresholds for toluene are highly variable and have been reported to range from as low as 0.016 ppm to 69.2 ppm (0.06 to 260 mg/m^3) (van Gemert, 1999; AIHA, 1989; WHO, 1986; Amoore and Hautala, 1983).

Adverse effects on the CNS are the critical effects of concern following acute human inhalation exposure to toluene (ATSDR, 2000). Symptoms of acute exposure progress from fatigue, headache and decreased manual dexterity to narcosis with increasing exposure levels. Depression, memory loss, impaired coordination and reaction time also occur as exposure levels increase (ACGIH, 1992). Respiratory tract irritation is also commonly reported in acute inhalation studies with both humans and experimental animals. Performance deficits in tests of neurobehaviour have been observed in studies with human volunteers acutely exposed to controlled toluene concentrations of >50 ppm (188 mg/m^3) and in laboratory animals repeatedly exposed to >500 ppm (1,875 mg/m^3) toluene (ATSDR, 2000). In the human volunteer studies, 50 ppm appears to be a threshold. ACGIH (1992) has summarized the acute toxicity thresholds for toluene as follows. Inhalation of 100 to 200 ppm (375 to 750 mg/m^3) is associated with headaches and mild transient irritation of the upper respiratory tract; 400 ppm (1,500 mg/m^3) is associated with eye irritation, lacrimation and giddiness; 600 ppm (2,250 mg/m^3) with lethargy, giddiness and slight nausea; 800 ppm (3,000 mg/m^3) is associated with moderate to severe eye and upper respiratory tract irritation, drowsiness, nasal discharge, ataxia, dizziness and metallic taste in the mouth. In a review of the available occupational studies, ACGIH (1992) concluded that the highest toluene air concentrations that can be tolerated for short durations (3.5 to 6 hours) without measurable neurobehavioural effects were 80 to 100 ppm (300 to 375 mg/m^3).

Current occupational exposure limits for toluene are based on human studies where CNS toxicity and irritant effects were demonstrated at air concentrations above 40 ppm (150 mg/m^3) (ACGIH, 1992).

It is well established that neurotoxicity and neurobehavioural deficits are the principal effects of long term inhalation exposure to toluene in both humans and experimental animals. Although there is a high degree of variability in the methods used, and the endpoints evaluated in the available studies, and most human studies suffer from a number of limitations, both the human and animal subchronic and chronic inhalation data generally indicate that no adverse neurological or neurobehavioural effects are likely to occur at toluene air concentrations lower than around 50 ppm (188 mg/m^3). The major symptoms following subchronic or chronic inhalation exposure to toluene in humans include subtle changes in neurological functions including cognitive and neuromuscular performance, hearing and colour discrimination in chronically exposed workers. Subchronic or chronic studies with experimental animals also indicate that major symptoms of toluene exposure include behavioural changes, hearing loss and subtle changes in brain structure, brain electrophysiology and brain chemistry. Studies of occupationally exposed workers also indicate that chronic exposure to toluene concentrations ranging from 30 to 130 ppm (113 to 488 mg/m^3) can lead to deficits in hearing and colour vision. Hearing loss has also been reported in experimental animals exposed to 700 to 1,500 ppm (2,625 to 5,625 mg/m^3) toluene (ATSDR, 2000).

The limited human data on reproductive and developmental effects of toluene does not provide convincing evidence that toluene causes reproductive effects in humans (ATSDR, 2000). A number of developmental toxicity studies with rats, mice and rabbits exposed *via* inhalation to toluene indicate that toluene is not a potent teratogen at exposure levels below those that induce maternal toxicity, but it can retard fetal growth and skeletal development and cause behavioural alterations in offspring (ATSDR, 2000). It should also be recognized that the available developmental toxicity studies are limited by issues such as unknown or unconventional exposure durations, poorly quantified exposures, co-exposure to other solvents, inadequate descriptions of maternal toxicity, use of individual offspring instead of litters for statistical analyses and unknown purity of toluene used (Donald *et al.*, 1991).

All of the short-term guideline values summarized in Table 11 are considerably lower than the apparent human effects threshold of 50 ppm (188 mg/m^3). Therefore, all these values appear to be adequately protective of human health over their respective averaging periods. All the long-term values in Table 11 are well below the subchronic, chronic and reproductive and developmental NOAEL and LOAEL values reported in the scientific literature. Thus, all the long-term air quality guideline values also appear to be adequately protective of human health.

It should be recognized that most air quality guidelines in Table 11 have the built-in assumption that all human exposure to toluene occurs *via* inhalation. They do not account for other sources, pathways and routes of toluene exposure. If exposure were apportioned to reflect these, the values presented in Table 11 would decrease in proportion to the magnitude of the exposure from these other sources, pathways and routes. However, one notable exception to this is the Massachusetts jurisdiction. MDEP (1995) states that the ATCs are roughly equivalent to the U.S. EPA reference concentration (RfC), but are derived from the threshold effects exposure limit (TEL) representing 20% of an allowable exposure. The ATC thus corresponds to five times the TEL. None of the other jurisdictions reviewed discuss exposure apportionment with respect to toluene air quality guidelines in their available documentation.

In addition, none of the agencies with air quality guidelines in Table 11 reported any special consideration of children or other sensitive individuals in air quality guideline development.

Based on the information reviewed, none of the agencies listed in Table 11 specifically acknowledged an ecological component in the development of air quality guidelines for toluene.

In addition, given the available data on the environmental fate, transport and effects of toluene, this compound is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone or alter precipitation patterns. No specific information on the photochemical smog formation potential of toluene was identified; however, it would be expected to have a similarly low to moderate smog formation potential as ethylbenzene and xylenes.

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APPENDIX A

REVIEW OF AIR QUALITY GUIDELINES FOR TOLUENE USED BY AGENCIES IN NORTH AMERICA AND ELSEWHERE

Agency:

California Environmental Protection Agency (Cal EPA), Office of Environmental Health Hazard Assessment (OEHHA)

Guideline Value(s):

Acute reference exposure level (REL) = 37,000 $\mu g/m^3$.
Level Protective of Severe Adverse Effects = 19,000 $\mu g/m^3$.
Chronic reference exposure level (REL) = 300 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

Acute REL = one-hour averaging time.
Chronic REL = continuous exposure (daily exposure over a lifetime).

Application / How Guideline is Used by Agency:

RELs are for use in facility health risk assessments conducted for the AB 2588 Air Toxics "Hot Spots" Program.

Scientific Basis for Guideline Development:

The acute REL was derived from a NOAEL of 40 ppm for mild central nervous system effects and irritation of the eyes and respiratory tract in human males Critical effects included impaired reaction time and symptoms of headache, dizziness, a feeling of intoxication, and slight eye and nose irritation. The Cal EPA adjusted the NOAEL for one-hour exposure duration and applied an uncertainty factor of 10 to account for intraspecies variation.

The airborne level of toluene that is protective against severe adverse effects was based on a NOAEL of 500 ppm for fetotoxicity reported in IRDC (1985). An uncertainty factor of 100 was applied to the NOAEL to account for animal to human extrapolation and for intraindividual variability (10-fold each).

The chronic REL was developed from a NOAEL of 40 ppm for nervous system, respiratory system, and development effects in rats. Critical effects included decreased brain (subcortical limbic area) weight, and altered dopamine receptor (caudate-putamen) binding. The Cal EPA converted the NOAEL to an average experimental concentration based on the experimental exposure duration and applied an uncertainty factor of 100 to account for the subchronic duration of the aforementioned study and intraspecies variation.

Status of Guideline (Date of Last Revision or Update):

Acute REL = March, 1999.
Chronic REL = August, 2003.

Additional Comments:

n/a

References and Supporting Documentation:

California Environmental Protection Agency (Cal EPA). 1999. Acute Toxicity Summary for Toluene. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment URL: http://www.oehha.org/air/acute_rels/allAcRELs.html (accessed 11 November 2003).

California Environmental Protection Agency (Cal EPA). 2003. Chronic Toxicity Summary for Toluene. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment URL: http://www.oehha.org/air/chronic_rels/AllChrels.html (accessed 11 November 2003).

Agency:

Health Canada.

Guideline Value(s):

Tolerable concentration (TC) = 3,750 µg/m^3.

Averaging Time to Which Guideline Applies:

Continuous exposure (daily exposure over a lifetime).

Application / How Guideline is Used by Agency:

The government of Canada states that TCs provide a health-based goal to which levels of various pollutants generally indoor or ambient air can be compared. TCs are generally airborne concentrations to which it is believed that a person can continuously be exposed to over a lifetime without deleterious effect.

Scientific Basis for Guideline Development:

The government of Canada developed this TC from the lowest NOAEL of 150 mg/m^3 based on decreased neurological function, increased neurological symptoms, and respiratory tract irritation in an adequate clinical study in human volunteers. The NOAEL was converted from six-hour daily dosing to continuous exposure and an uncertainty factor of 10 was applied to account for intraspecies variation.

Status of Guideline (Date of Last Revision or Update):

June 1991.

Additional Comments:

n/a

References and Supporting Documentation:

Health Canada. 1996. Health-Based Tolerable Daily Intakes/ Concentrations and Tumorigenic Doses/ Concentrations for Priority Substances. Government of Canada, Health Canada, Environmental Health Directorate, Health Protection Branch. Ottawa, ON.

Meek, M.E. and P.K.L. Chan. 1994. Toluene: Evaluation of Risks to Health from Environmental Exposure in Canada. In: Environmental Carcinogenesis and Ecotoxicology Reviews, Part C of Journal of Environmental Science and Health. C12(2): 507-515.

Government of Canada. 1999. Canadian National Ambient Air Quality Objectives (NAAQOs): Process and Status. Government of Canada, Environment Canada, Canadian Council of Ministers of the Environment (CCME). Ontario, Canada.

Government of Canada. 2003. Priority Substance Lists (PSLs). Government of Canada, Environment Canada, CEPA Environmental Registry. URL: http://www.ec.gc.ca/CEPARegistry/subs_list/Priority.cfm (accessed 13 November 2003).

Agency:

Louisiana Department of Environmental Quality (DEQ).

Guideline Value(s):

Ambient air standard (AAS) = 8,900 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

Eight-hour averaging time.

Application / How Guideline is Used by Agency:

AASs are used by Louisiana DEQ to review permit applications for stationary sources that emit toluene to the atmosphere.

Scientific Basis for Guideline Development:

Scientific basis was not provided.

Status of Guideline (Date of Last Revision or Update):

October 2003.

Additional Comments:

Louisiana DEQ classifies toluene as an acute and chronic (non-carcinogenic) toxin.

References and Supporting Documentation:

Louisiana Department of Environmental Quality (DEQ). 2003. Title 33 Environmental Quality, Part III Air, Chapter 51: Comprehensive Toxic Air Pollutant Emission Control Program. Louisiana Department of Environmental Quality (DEQ). Baton, LA.

Agency:

Massachusetts Department of Environmental Protection (DEP).

Guideline Value(s):

Threshold effects exposure level (TEL) = 80 $\mu g/m^3$.
Allowable ambient limit (AAL) = 20 $\mu g/m^3$.
Allowable threshold concentration (ATC) = 400 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

TEL = 24-hour averaging time.
AAL = annual averaging time.
ATC = continuous exposure (daily exposure over a lifetime).

Application / How Guideline is Used by Agency:

The TEL and AAL guidelines are to be employed in the permitting, compliance, and enforcement of the MA DEP air quality program. The primary goal of the TELs and the AALs developed by MA DEP is to protect public health from any air contaminant causing known or potentially deleterious effects. These guidelines were developed without regard to production volume, exposure level, regulatory implication, economic considerations, or control technology issues.

Scientific Basis for Guideline Development:

TELs are developed using either an occupational limit or, when a reference concentration (RfC) is published by the U.S. EPA IRIS, an RfC where appropriate and defensible. In the case of toluene, an RfC of 0.4 mg/m^3 was established by the U.S. EPA. This RfC was then divided by five to account for exposure through media other than air based on an assumption that ambient air contributes only 20% of the total exposure. The TEL is derived in such a manner considering children to be the most sensitive potential receptor.

In the case of toluene, the AAL was based on the non-threshold effect exposure level (NTEL) as the NTEL was lower than the TEL of 80 $\mu g/m^3$. The NTEL was calculated from the RfC of 0.4 mg/m^3 by applying a non-threshold effects uncertainty factor of 20 which accounts for observed structure relationships analysis weight-of-evidence. No adjustments were made for multimedia considerations.

ATCs are roughly equivalent to the U.S. EPA reference concentration (RfC), but are derived from the threshold effects exposure limit (TEL) representing 20% of an allowable exposure. The ATC thus corresponds to five times the TEL. ATCs are an air concentration that would not be expected to result in adverse non-carcinogenic health effects. The ATC is derived considering acute and chronic threshold health endpoints, including reproductive effects.

Status of Guideline (Date of Last Revision or Update):

December 1995.

Additional Comments:

n/a

References and Supporting Documentation:

Massachusetts Department of Environmental Protection (DEP). 1995. Massachusetts Allowable Threshold Concentrations (ATCs). Commonwealth of Massachusetts, Executive Office of Environmental Affairs, Department of Environmental Protection. Boston, MA.

Agency:

Michigan Department of Environmental Quality (DEQ).

Guideline Value(s):

Initial threshold screening level (ITSL) = 400 µg/m^3.

Averaging Time to Which Guideline Applies:

ITSL = 24-hour averaging time.

Application / How Guideline is Used by Agency:

Michigan air toxic rules require that each source must apply the best available control technology for toxics T-BACT) and that the emissions of the toxic air contaminant cannot result in a maximum ambient concentration that exceeds the applicable health based screening levels (*i.e.*, ITSL, IRSL, or SRSL). ITSLs are required for any new or modified emissions source or sources for which a permit to install is requested and which emits a toxic air contaminant.

Scientific Basis for Guideline Development:

The ITSL was based on the reference concentration (RfC) of 400 µg/m^3 for neurological effects established by the U.S. EPA.

Status of Guideline (Date of Last Revision or Update):

August 1992.

Additional Comments:

The Initial Threshold Screening Level (ITSL) is defined as the health based screening level for non-carcinogenic effects of a toxic air contaminant. It is determined by a number of different methods, depending upon the available toxicological data. The rules specify a hierarchy of methods for determining the ITSL. There are two health based screening levels for carcinogenic effects. These include the Initial Risk Screening Level (IRSL), which is defined as an increased cancer risk of one in one million (10-6), and the Secondary Risk Screening Level (SRSL), which is defined as an increased cancer risk of one in one hundred thousand (10-5). The IRSL applies only to the new or modified source subject to the permit application. If the applicant cannot demonstrate that the emissions of the toxic air contaminant meet the IRSL, they may choose to demonstrate compliance with the SRSL, however in this case they must include all sources of that toxic air contaminant emitted from the plant, not just the emission unit being permitted.

References and Supporting Documentation:

Michigan Department of Environmental Quality (DEQ). 2003. Final Screening Level List. Table 2. Michigan Department of Environmental Quality (DEQ). Air Quality Division. URL: http://www.michigan.gov/deq/0,1607,7-135-3310_4105---,00.html (accessed 12 November 2003).

Michigan Department of Environmental Quality (DEQ). 2002. Procedures for Developing Screening Levels. Michigan Department of Environmental Quality (DEQ). Air Quality Division. Lansing, Michigan.

Agency:

Minnesota Department of Health (MDH).

Guideline Value(s):

Acute health risk value (HRV) = 37,000 $\mu g/m^3$.
Chronic health risk value (HRV) = 400 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

Acute HRVs are comparable to a one-hour averaged concentration of chemicals or defined mixtures of chemicals in air. Chronic HRVs are comparable to an annual average concentration of chemicals or defined mixtures of chemicals in air.

Application / How Guideline is Used by Agency:

HRVs are used by the MDH and sister agencies such as the Minnesota Pollution Control Agency, to assist in the assessment of potential health risks associated with chemicals in ambient air. HRVs may also be used as one set of criteria for assessing risks in the environmental review process, issuing air permits, risk assessments, and other site-specific assessments.

Scientific Basis for Guideline Development:

HRVs were derived using the best peer-reviewed science and public health policies available at the time of their development. Uncertainty values were incorporated to ensure that the HRVs present minimal risk to human health. The acute HRV specific to toluene was based on nervous system effects and eye and respiratory system irritation. The chronic HRV specific to toluene was based on nervous system and upper respiratory system effects.

Status of Guideline (Date of Last Revision or Update):

August 2003.

Additional Comments:

The approaches used to develop HRVs are considered conservative (*i.e.*, by design they err in the direction of protecting public health); thus, the MDH is confident that exposures to chemicals in concentrations at or below the HRVs present minimal risk to human health. In addition, because of MDH's conservative approach, exposures to chemical concentrations above HRVs do not necessarily pose a public health risk.

References and Supporting Documentation:

Minnesota Department of Health (MDH). 2003. Health Risk Values for Air. Minnesota Department of Health (MDH), Environmental Health in Minnesota. URL: http://www.health.state.mn.us/divs/eh/air/hrvtablepr.htm (accessed 12 November 2003).

Agency: Netherlands Research for Man and Environment (RIVM).
Guideline Value(s): Tolerable concentration in air (TCA) = 400 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: Not provided.
Scientific Basis for Guideline Development: The TCA was based on the reference concentration (RfC) of 400 $\mu g/m^3$ for neurological effects established by the U.S. EPA.
Status of Guideline (Date of Last Revision or Update): March 2001.
Additional Comments: TCAs are a type of maximum permissible risk level (MPR) specific to inhalation exposure. MPRs are defined as the amount of a substance (usually a chemical substance) that any human individual can be exposed to daily during full lifetime without significant health risk.
References and Supporting Documentation: Research for Man and Environment (RIVM). 2001. RIVM Report 711701 025 Re-evaluation of Human-toxicological Maximum Permissible Risk Levels. URL: http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf (accessed 13 November 2003).

Agency:

Newfoundland and Labrador Air Pollution Control Regulations.

Guideline Value(s):

24-hour air quality standard (AQS) = 2,000 $\mu g/m^3$.
One-hour point of impingement (POI) = 1,600 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

See above.

Application / How Guideline is Used by Agency:

The minister under the Executive Council Act uses the values prescribed in the Criteria for Acceptable Air Quality for controlling air quality, where the amount of air contaminants in the atmosphere due to all sources shall not exceed these values (*i.e.*, AQS). Point of impingement values are used as the standard for concentrations of air contaminants from a stationary source at the point of impingement that shall not be exceeded.

Scientific Basis for Guideline Development:

Scientific basis was not provided.

Status of Guideline (Date of Last Revision or Update):

May 2003.

Additional Comments:

n/a

References and Supporting Documentation:

Newfoundland and Labrador Air Pollution Control Regulations. 2003. Newfoundland and Labrador Regulation 56/03. Government of Newfoundland and Labrador, Queen's Printer, May 2003.

Agency: New Hampshire Department of Environmental Services (DES).
Guideline Value(s): 24-hour ambient air limit (AAL) = 671 $\mu g/m^3$. Annual ambient air limit (AAL) = 400 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: AALs are used by the New Hampshire DES to review permit applications for sources that emit toluene to the atmosphere. Sources are regulated through a state-wide air permitting system and include any new, modified, or existing stationary source, area source, or device.
Scientific Basis for Guideline Development: The 24-hour AAL is derived from the threshold limit value time weighted average (TLV-TWA) of 50 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. The New Hampshire DES applied a time adjustment factor of 2.8 and a safety factor of 100 to the TLV-TWA. The annual AAL was based on the reference concentration (RfC) of 400 $\mu g/m^3$ for neurological effects established by the U.S. EPA.
Status of Guideline (Date of Last Revision or Update): March 1997.
Additional Comments: n/a
References and Supporting Documentation: New Hampshire Department of Environmental Services (DES). New Hampshire Code of Administrative Rules. Chapter Env-A 1400. Regulated Toxic Air Pollutants. New Hampshire Department of Environmental Services (DES). Concord, NH.

Agency:

New Jersey Department of Environmental Protection (DEP).

Guideline Value(s):

Short-term reference concentration (RfC) = 37,000 μg/m^3.
Reference concentration (RfC) = 400 μg/m^3.

Averaging Time to Which Guideline Applies:

Short-term RfC = one-hour averaging time.
RfC = continuous exposure (daily exposure over a lifetime).

Application / How Guideline is Used by Agency:

RfCs are used by the New Jersey DEP to review permit applications for sources that emit toluene to the atmosphere.

Scientific Basis for Guideline Development:

The 24-hour RfC is derived from the acute REL of 37,000 μg/m^3 for mild central nervous system effects and irritation of the eyes and respiratory tract established by the Cal EPA.

The RfC for toluene is based on the reference concentration of 1,000 μg/m^3 for neurological effects established by the U.S. EPA.

Status of Guideline (Date of Last Revision or Update):

April 2003.

Additional Comments:

n/a

References and Supporting Documentation:

New Jersey Department of Environmental Protection (DEP). 2003. Reference Concentrations for Short-Term Inhalation Exposure. New Jersey Department of Environmental Protection (DEP), Division of Air Quality, Bureau of Air Quality Evaluation. April, 2003.

New Jersey Department of Environmental Protection (DEP). 1994. Technical Manual 1003: Guidance on Preparing a Risk Assessment for Air Contaminant Emissions. New Jersey Department of Environmental Protection (DEP), Air Quality Permitting Program, Bureau of Air Quality Evaluation. Revised December 1994.

Agency:

New York State Department of Environmental Conservation (DEC).

Guideline Value(s):

Short-term guideline concentration (SGC) = 37,000 $\mu g/m^3$.
Annual guideline concentration (AGC) = 400 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

SGC = one-hour averaging time.
AGC = continuous exposure (daily exposure over a lifetime).

Application / How Guideline is Used by Agency:

SGCs and AGCs are used by the New York State DEC to review permit applications for sources that emit toluene to the atmosphere.

Scientific Basis for Guideline Development:

The SGC for toluene was independently derived by the NY State DEC to protect the general population from adverse inhalation exposure at off-site industrial property. The specific scientific basis was not provided.

The AGC for toluene was based on the reference concentration (RfC) of 400 $\mu g/m^3$ for neurological effects established by the U.S. EPA.

Status of Guideline (Date of Last Revision or Update):

July 2000.

Additional Comments:

n/a

References and Supporting Documentation:

New York State Department of Environmental Conservation (DEC). 2000. DAR – 1 AGC/SGC Tables includes TLVs & STELs for the Year 2000. New York State Department of Environmental Conservation, Division of Air Resources, Bureau of Stationary Sources. Albany, NY.

Agency: North Carolina Department of Environment and Natural Resources (DENR).
Guideline Value(s): One-hour toxic air pollutant guideline (TAPG) = 56 mg/m^3 (56,000 μg/m^3). 24-hour toxic air pollutant guideline (TAPG) = 4.7 mg/m^3 (4,700 μg/m^3).
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: TAPGS are used by the North Carolina DENR to review permit applications for sources that emit toluene to the atmosphere.
Scientific Basis for Guideline Development: Scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): April 2001.
Additional Comments: n/a
References and Supporting Documentation: North Carolina Department of Environment and Natural Resources (ENR). 2002. North Carolina Air Quality Rules 15A NCAC 2D (Air Pollution Control Requirements) and 15A NCAC 2Q (Air quality Permit Procedures). Section .1100 – Control of Toxic Air Pollutants. North Carolina Department of Environment and Natural Resources. Raleigh, NC.

Agency: Ohio Environmental Protection Agency (EPA)
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Ohio Environmental Protection Agency (EPA). 2002. Review of New Sources of Air Toxic Emissions. Option A. Ohio Environmental Protection Agency, Division of Air Pollution Control. Columbus, Ohio.

Agency:

Oklahoma Department of Environmental Quality (DEQ).

Guideline Value(s):

Maximum acceptable ambient air concentration (MAAC) = 37,668 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

24-hour averaging time.

Application / How Guideline is Used by Agency:

MAACs are used by Oklahoma DEQ to review permit applications of sources that emit toluene to the atmosphere.

Scientific Basis for Guideline Development:

The 24-hour MAAC was based on the recommended exposure limit time weighted average (REL-TWA) of 100 ppm established by the National Institute for Occupational Safety and Health (NIOSH). A safety factor of 10 was incorporated by the Oklahoma DEQ.

Status of Guideline (Date of Last Revision or Update):

November 2003.

Additional Comments:

n/a

References and Supporting Documentation:

Oklahoma Department of Environmental Quality (DEQ). 2003. Total Air Toxics Partial Listing. Oklahoma Department of Environmental Quality. URL: http://www.deq.state.ok.us/AQDnew/toxics/listings/pollutant_query_1.html (accessed 12 November 2003).

Oklahoma Department of Environmental Quality (DEQ). Title 252. Department of Environmental Quality Chapter 100. Air Pollution Control. 100:252-41: Control of Emission of Hazardous and Toxic Air Contaminants. Oklahoma Department of Environmental Quality. Oklahoma City, OK.

Agency:

Ontario Ministry of Environment and Energy (OMOE).

Guideline Value(s):

24-hour ambient air quality criteria (AAQC) = 2,000 μg/m^3.
Half-hour point of impingement (POI) = 2,000 μg/m^3.

Averaging Time to Which Guideline Applies:

See above.

Application / How Guideline is Used by Agency:

AAQCs are used by OMOE to represent human health or environmental effect-based values not expected to cause adverse effects based on continuous exposure. AAQCs are not used by OMOE to permit stationary sources that emit toluene into the environment. The 30-minute POI is used by OMOE to review permit applications for stationary sources that emit toluene to the environment.

Scientific Basis for Guideline Development:

The AAQC and the POI for toluene were both derived based on odour effects, where the odour thresholds range from 600 to 140,000 μg/m^3 and the geometric mean is 6,000 μg/m^3.

Status of Guideline (Date of Last Revision or Update):

March 2001.

Additional Comments:

The half-hour POI for toluene is defined as an air quality standard by OMOE.

References and Supporting Documentation:

Ontario Ministry of Environment and Energy (OMOE). 2001. Summary of Point of Impingement Standards, Point of Impingement Guidelines, and Ambient Air Quality Criteria (AAQCs). Standards Development Branch, Ontario Ministry of the Environment, September 2001.

Ontario Ministry of Environment and Energy (OMOE). 2001. Ontario Air Standards for Toluene. Standards Development Branch, Ontario Ministry of the Environment, March 2001.

Agency:

Quebec Ministry of Environment.

Guideline Value(s):

Maximum 15-minute air quality criteria (MAQC) = 1,000 $\mu g/m^3$.
Maximum annual air quality criteria (MAAQC) = 400 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

See above.

Application / How Guideline is Used by Agency:

MAQCs and MAAQCs are taken into account in the determination of the allowed quantity of a substance in the ambient air and in the exposure received from drinking water, food or other sources.

Scientific Basis for Guideline Development:

The 15-minute MAQC for toluene is based on the 30-minute exposure duration guideline value of 1,000 $\mu g/m^3$ for odour annoyance established by the WHO.

The MAAQC is based on the reference concentration (RfC) of 400 $\mu g/m^3$ for neurological effects established by the U.S. EPA.

Status of Guideline (Date of Last Revision or Update):

May 2002.

Additional Comments:

n/a

References and Supporting Documentation:

Government of Quebec. 2002. Air Quality Criteria. Government of Quebec, Ministry of the Environment. URL: http://www.menv.gouv.qc.ca/air/criteres/fiches.pdf (accessed 13 November 2003).

Agency:

Texas Natural Resource Conservation Commission (TNRCC).

Guideline Value(s):

Short-term effects screening level (ESL) = 1,880 μg/m^3.
Long-term effects screening level (ESL) = 188 μg/m^3.

Averaging Time to Which Guideline Applies:

Short-term ESL = one-hour averaging time.
Long-term ESL = annual averaging time.

Application / How Guideline is Used by Agency:

ESLs are used to evaluate the potential for effects to occur as a result of exposure to concentrations of constituents in the air. ESLs are based on data concerning health effects, odour nuisance potential, effects with respect to vegetation, and corrosion effects. They are not ambient air standards. If predicted or measured airborne levels of a constituent do not exceed the screening level, adverse health or welfare effects would not be expected to result. If ambient levels of constituents in air exceed the screening levels, it does not necessarily indicate a problem, but rather, triggers a more in-depth review.

Scientific Basis for Guideline Development:

Both the short-term and long-term ESLs for toluene were developed based on the threshold limit value time weighted average (TLV-TWA) of 50 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. Safety factors of 100 and 1,000 were applied by TNRCC to the short-term and long-term ESLs, respectively.

Status of Guideline (Date of Last Revision or Update):

October 2003.

Additional Comments:

n/a

References and Supporting Documentation:

Texas Natural Resource Conservation Commission (TNRCC). 2003. Effects Screening Levels List. URL: http://www.tnrcc.state.tx.us/permitting/tox/esl.html (accessed 13 November 2003).

Agency:

U.S. Agency for Toxic Substances and Disease Registry (ATSDR).

Guideline Value(s):

Acute minimum risk level (MRL) = 1 ppm (3,760 μg/m^3).
Chronic minimum risk level (MRL) = 0.08 ppm (301 μg/m^3).

Averaging Time to Which Guideline Applies:

Acute exposure durations are based on exposure durations ranging from one to 14 days.
Chronic exposure durations are based on exposure durations equivalent to or greater than 365 days (*i.e.*, one year).

Application / How Guideline is Used by Agency:

MRLs are intended to serve as a screening tool to be used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. MRLs are not intended to define clean-up or action levels for ATSDR or other Agencies.

Scientific Basis for Guideline Development:

The acute MRL was developed from a NOAEL of 40 ppm based on neurological effects in humans. The ATSDR adjusted the NOAEL from intermittent to continuous exposure and applied an uncertainty factor of 10 to account for intraspecies variation.

The chronic MRL is based on a LOAEL of 35 ppm toluene for colour vision impairment in shoemakers reported by Zavalic *et al.* (1998a). This LOAEL was adjusted for continuous exposure [LOAEL x 8/24 x 5/7] and an uncertainty factor of 100 (10 for the use of a LOAEL; 10 to account for human variability).

Status of Guideline (Date of Last Revision or Update):

August 2000.

Additional Comments:

MRLs are an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects.

References and Supporting Documentation:

U.S. Agency for Toxic Substances and Disease Registry (ATSDR). 2000. Toxicological profile for toluene. URL: http://www.atsdr.cdc.gov/toxpro2.html (accessed on 11 November 2003).

Agency:

U.S. Environmental Protection Agency (EPA).

Guideline Value(s):

Reference concentration (RfC) = 400 μg/m^3.

Averaging Time to Which Guideline Applies:

Continuous exposure (daily exposure over a lifetime).

Application / How Guideline is Used by Agency:

The RfC was developed for use by the U.S. EPA staff in risk assessments, decision-making, and regulatory activities.

Scientific Basis for Guideline Development:

The RfC was developed from a LOAEL of 332 mg/m^3 based on neurological effects in an occupational study. A safety factor of 300 was applied by the U.S. EPA to the study's LOAEL to account for intraspecies variability, the use of a LOAEL, and to account for data base deficiencies, including the lack of data and well-characterized laboratory animal exposures evaluating neurotoxicity and respiratory irritation.

Status of Guideline (Date of Last Revision or Update):

April 1992.

Additional Comments:

Toluene has not been classified for human carcinogenicity by the U.S.EPA.

The Integrated Risk Information System (IRIS) is an electronic database containing information pertaining to human health effects that may result from environmental exposure to a variety of chemicals. IRIS is prepared and maintained by the U.S. Environmental Protection Agency (EPA).

References and Supporting Documentation:

U.S. Environmental Protection Agency (EPA). 2003. Integrated Risk Information System (IRIS). URL: http://www.epa.gov/iris/index.html (accessed 11 November 2003).

Agency:

Vermont Agency of Natural Resources (ANR).

Guideline Value(s):

Short-term hazardous ambient air standard (HAAS) = 8,930 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

24-hour averaging time.

Application / How Guideline is Used by Agency:

HAASs are used by Vermont ANR to review permit applications for stationary sources that emit toluene to the atmosphere.

Scientific Basis for Guideline Development:

The 24-hour HAAS is based on the recommended exposure limit time weighted average (REL-TWA) of 100 ppm established by the National Institute for Occupational Safety and Health (NIOSH) as an occupational air standard. Since toluene is associated with both short-term irritant effects and also some type of extended, but not chronic, effect, the Vermont ANR applied a time factor of 4.2 to the REL-TWA to extrapolate to a continuous level. In addition, a safety factor of 10 was incorporated by the Vermont ANR.

Status of Guideline (Date of Last Revision or Update):

November 2001.

Additional Comments:

The Vermont ANR classified toluene as a non-carcinogen considered to have only short-term irritant effects.

References and Supporting Documentation:

Vermont Agency of Natural Resources (ANR). 2001. Air Pollution Control Regulations, Including Amendments to the Regulations Through: November 29, 2001. Vermont Agency of Natural Resources, Air Pollution Control Division, Department of Environmental Conservation, Agency of Natural Resources. Waterbury, Vermont.

Agency: Washington Department of Ecology (DOE).
Guideline Value(s): Acceptable source impact level (ASIL) = 400 μg/m^3.
Averaging Time to Which Guideline Applies: 24-hour averaging time.
Application / How Guideline is Used by Agency: ASILs are used Washington DOE to review permit applications for stationary sources that emit toluene to the atmosphere.
Scientific Basis for Guideline Development: The 24-hour ASIL for toluene is based on the reference concentration (RfC) of 400 μg/m^3 for neurological effects established by the U.S. EPA
Status of Guideline (Date of Last Revision or Update): October 1998.
Additional Comments: n/a
References and Supporting Documentation: Washington Department of Ecology (DOE). 1998. Chapter 173-460 WAC. Controls for New Sources of Toxic Air Pollutants. Washington Department of Ecology (DOE). Olympia, WA.

Agency:

World Health Organization (WHO).

Guideline Value(s):

30-minute guideline value (GV) = 1,000 μg/m^3.
One-week guideline value (GV) = 260 μg/m^3.

Averaging Time to Which Guideline Applies:

See above.

Application / How Guideline is Used by Agency:

The GVs were developed to provide background information which enables countries to set their national or regional air quality standards in the context of existing environmental, social, economic and cultural conditions.

Scientific Basis for Guideline Development:

The 30-minute GV developed for toluene was based on an odour threshold of 1,000 μg/m^3. No safety factors were applied by WHO.

The one-week GV was derived from a LOAEL of 332 mg/m^3 for central nervous system effects in occupationally exposed workers. WHO applied an uncertainty factor of 1,260 to the LOAEL.

Status of Guideline (Date of Last Revision or Update):

n/a

Additional Comments:

n/a

References and Supporting Documentation:

World Health Organization (WHO). 1999. Air Quality Guidelines. Chapter 3: Health-based Guidelines. World Health Organization, Geneva.